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(54) Title: TREATMENT OF CNS DISORDERS USING CNS TARGET MODULATORS

(57) Abstract: The invention is directed to compositions used for treating Central Nervous System (CNS) disorders. In addition, the invention provides convenient methods of treatment of a CNS disorder. Furthermore, the invention provides methods of treating sleep disorders using compositions that remain active for a discrete period of time to reduce side effects. More specifically, the invention is directed to the compositions and use of derivatized, *e.g.*, ester or carboxylic acid derivatized, antihistamine antagonists for the treatment of sleep disorders.

TREATMENT OF CNS DISORDERS USING CNS TARGET MODULATORS

REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Application Attorney Docket Number HPZ-001-1, Application Serial No. 60/329,701, filed on October 16, 2001, entitled "Treatment of CNS Disorders Using CNS Target Modulators"; pending U.S. Provisional Patent Application Attorney Docket Number HPZ-001-2, Application Serial No. 60/381,507, filed on May 17, 2002, entitled "Treatment of CNS Disorders Using CNS Target Modulators"; pending U.S. Provisional Patent Application Attorney Docket Number HPZ-001-3, filed on September 27, 2002, entitled "Treatment of CNS Disorders Using CNS Target Modulators"; and pending U.S. Provisional Patent Application Attorney Docket Number HPZ-001-4, filed on even date herewith, entitled "Treatment of CNS Disorders Using CNS Target Modulators" the entire contents of each of the above-identified applications, which are hereby incorporated herein by reference.

BACKGROUND OF THE INVENTION

Difficulties in falling asleep, remaining asleep, sleeping for adequate lengths of time, or abnormal sleep behavior are common symptoms for those suffering with a sleep disorder. A number of sleep disorders, *e.g.*, insomnia or sleep apnea, are described in the online Merck Manual of Medicinal Information.

Current treatment of many sleep disorders include the use of prescription hypnotics, *e.g.*, benzodiazapines, that may be habit-forming, lose their effectiveness after extended use, and metabolize more slowly for certain designated groups, *e.g.*, elderly persons, resulting in persisting medicative effects.

Other, more mild manners of treatment include over-the-counter antihistamines, *e.g.*, diphenhydramine or dimenhydrinate, which are not designed to be strictly sedative in their activity. This method of treatment is also associated with a number of adverse side effects, *e.g.*, persistence of the sedating medication after the prescribed time of treatment, or the so-called "hangover effect". Many of these side effects result from nonspecific activity in both the periphery as well as the Central Nervous System (CNS) during this period of extended medication.

SUMMARY OF THE INVENTION

A need exists for the development of new compositions used for the improved treatment of sleep disorders that remain active for a discrete period of time to reduce side effects, such as the "hangover effect." The strategy of treatment is applicable to a broader array of CNS targets.

Therefore, the invention is directed to compositions used for treating Central Nervous System (CNS) disorders. In addition, the invention provides convenient methods of treatment of a CNS disorder. Furthermore, the invention provides methods of treating sleep disorders using compositions that remain active for a discrete period of time to reduce side effects. More specifically, the invention is directed to the compositions and use of derivatized, *e.g.*, ester or carboxylic acid derivatized, antihistamine antagonists for the treatment of sleep disorders.

Thus, in one aspect of the invention, the invention is a method of treating a sleep disorder. The method comprises administering an effective amount of an antihistamine compound, such that the sleep disorder is treated, wherein the antihistamine compound has a favorable biological property (FBP).

An additional aspect of the invention is a method of treating a Central Nervous System (CNS) disorder. The method comprises administering an effective amount of a therapeutic compound to a subject, such that the therapeutic compound penetrates into the CNS and modulates the CNS target to treat the CNS disorder. Accordingly, the therapeutic compound can have the formula:

$$[CA]\text{-}(SP)_n\text{-}[DA]$$

wherein CA is a moiety that modulates an active CNS target receptor or a collection of active CNS target receptors, DA is a drug activity modulating moiety that provides the ability to modulate the activity of the therapeutic compound, *e.g.*, ester or carboxylic acid, SP is a spacer molecule, and n is 0 or 1.

Another aspect of the invention is a method of treating a Central Nervous System (CNS) disorder. The method comprises administering an effective amount of a therapeutic compound to a subject, such that the therapeutic compound penetrates into the CNS and modulates the CNS target to treat the CNS disorder. Accordingly, the therapeutic compound can have the formula:

$$[CA]\text{-}(SP)_n\text{-}[EG]$$

wherein CA is a moiety that modulates an active CNS target receptor or a collection of active CNS target receptors, EG is an ester group that modifies the half-life of the therapeutic compound, SP is a spacer molecule, and n is 0 or 1.

In a more specific aspect of the invention, the invention is directed to a method of treating a sleep disorder. The method comprises administering an effective amount of a therapeutic compound to a subject, such that the sleep disorder is treated. Accordingly, the therapeutic compound can have the formula:

$$[CA]\text{-}(SP)_n\text{-}[EG]$$

wherein CA is a moiety that modulates an active CNS target receptor or a collection of active CNS target receptors, EG is an ester group that modifies the half-life of the therapeutic compound, SP is a spacer molecule, and n is 0 or 1.

In an additional aspect, the invention is directed to a method of treating a sleep disorder target. The method comprises administering an effective amount of a therapeutic compound to a subject, such that the sleep disorder is treated. Accordingly, the therapeutic compound can have the formula:

$$[AD]\text{-}(SP)_n\text{-}[EG]$$

wherein AD is a moiety that agonizes an adenosine receptor or a collection of adenosine receptors, EG is an ester group that modifies the half-life of the therapeutic compound, SP is a spacer molecule, and n is 0 or 1.

Another aspect of the invention is directed to a method of treating a sleep disorder target. The method comprises administering an effective amount of a therapeutic compound to a subject, such that the sleep disorder is treated. Accordingly, the therapeutic compound can have the formula:

$$[AH]\text{-}(SP)_n\text{-}[DA]$$

wherein AH is a moiety that antagonizes a histamine receptor or a collection of histamine receptors, DA is a drug activity modulating moiety that provides the ability to modulate the activity of the therapeutic compound, SP is a spacer molecule, and n is 0 or 1.

In another aspect, the invention is directed to a method of treating a sleep disorder. The method comprises administering an effective amount of a therapeutic compound to a subject, such that the sleep disorder is treated. Accordingly, the therapeutic compound can have the formula:

$$[AH]-(SP)_n-[EG]$$

wherein AH is a moiety that antagonizes a histamine receptor or a collection of histamine receptors, EG is an ester group that modifies the half-life of the therapeutic compound, SP is a spacer molecule, and n is 0 or 1.

Another aspect of the invention is a method of modulating a sleep disorder target. The method comprises administering an effective amount of a therapeutic compound to a subject, such that the sleep disorder target is modulated, wherein the therapeutic compound comprises the formula:

$$[CA]-(SP)_n-[DA]$$

wherein CA is a moiety that modulates an active CNS target receptor or a collection of active CNS target receptors, DA is a drug activity modulating moiety that provides the ability to modulate the activity of the therapeutic compound, *e.g.*, ester or carboxylic acid, SP is a spacer molecule, and n is 0 or 1.

Another aspect of the invention is a method of modulating a sleep disorder target. The method comprises administering an effective amount of a therapeutic compound to a subject, such that the sleep disorder target is modulated, wherein the therapeutic compound comprises the formula:

$$[CA]-(SP)_n-[EG]$$

wherein CA is a moiety that modulates an active CNS target receptor or a collection of active CNS target receptors, EG is an ester group that modifies the half-life of the therapeutic compound, SP is a spacer molecule, and n is 0 or 1.

Another aspect of the invention is a method of modulating a sleep disorder target. The method comprises administering an effective amount of a therapeutic compound to a subject, such that the sleep disorder target is modulated, wherein the therapeutic compound comprises the formula:

$$[AD]-(SP)_n-[EG]$$

wherein AD is a moiety that agonizes an adenosine receptor or a collection of adenosine receptors, EG is an ester group that modifies the half-life of the therapeutic compound, SP is a spacer molecule, and n is 0 or 1.

Another aspect of the invention is a method of modulating a sleep disorder target. The method comprises administering an effective amount of a therapeutic compound to a subject, such that the sleep disorder target is modulated, wherein the therapeutic compound comprises the formula:

$$[AH]\text{-}(SP)_n\text{-}[DA]$$

wherein AH is a moiety that antagonizes a histamine receptor or a collection of histamine receptors, DA is a drug activity modulating moiety that provides the ability to modulate the activity of the therapeutic compound, *e.g.*, ester or carboxylic acid, SP is a spacer molecule, and n is 0 or 1.

Another aspect of the invention is a method of modulating a sleep disorder target. The method comprises administering an effective amount of a therapeutic compound to a subject, such that the sleep disorder target is modulated, wherein the therapeutic compound comprises the formula:

$$[AH]\text{-}(SP)_n\text{-}[EG]$$

wherein AH is a moiety that antagonizes a histamine receptor or a collection of histamine receptors, EG is an ester group that modifies the half-life of the therapeutic compound, SP is a spacer molecule, and n is 0 or 1.

One aspect of the invention is a Central Nervous System (CNS) disorder target modulator comprising the formula:

$$[CA]\text{-}(SP)_n\text{-}[DA]$$

wherein CA is a moiety that modulates an active CNS target receptor or a collection of active CNS target receptors, DA is a drug activity modulating moiety that provides the ability to modulate the activity of the therapeutic compound, *e.g.*, ester or carboxylic acid, SP is a spacer molecule, and n is 0 or 1.

Another aspect of the invention is a CNS disorder target modulator comprising the formula:

$$[CA]\text{-}(SP)_n\text{-}[EG]$$

wherein CA is a moiety that modulates an active CNS target receptor or a collection of active CNS target receptors, EG is an ester group that modifies the half-life of the therapeutic compound, SP is a spacer molecule, and n is 0 or 1.

Another aspect of the invention is a sleep disorder target modulator comprising the formula:

$$[CA]\text{-}(SP)_n\text{-}[EG]$$

wherein CA is a moiety that modulates an active CNS target receptor or a collection of active CNS target receptors, EG is an ester group that modifies the half-life of the therapeutic compound, SP is a spacer molecule, and n is 0 or 1.

In a another aspect of the invention a sleep disorder target modulator comprises the formula:

$$[AH]\text{-}(SP)_n\text{-}[DA]$$

wherein AH is a moiety that antagonizes a histamine receptor, DA is a drug activity modulating moiety that provides the ability to modulate the activity of the therapeutic compound, *e.g.*, ester or carboxylic acid, SP is a spacer molecule, and n is 0 or 1.

In a particular aspect of the invention a sleep disorder target modulator comprises the formula:

$$[AH]\text{-}(SP)_n\text{-}[EG]$$

wherein AH is a moiety that antagonizes a histamine receptor, EG is an ester group that modifies the half-life of the therapeutic compound, SP is a spacer molecule, and n is 0 or 1.

Another aspect of the invention is a pharmaceutical composition comprising a therapeutic compound as prepared according to the methodology of this invention, and a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE DRAWINGS

Figs. 1A-C are graphs depicting the effect of a compound of the invention on parameters pertinent to sleep disorders.

Figs. 2A-G are graphs depicting the binding of reference compounds to the receptors as indicated.

DETAILED DESCRIPTION OF THE INVENTION

The invention is directed to compositions used for treating Central Nervous System (CNS) disorders. In addition, the invention provides convenient methods of treatment of a CNS disorder. Furthermore, the invention provides methods of treating

sleep disorders using compositions that remain active for a discrete period of time to reduce side effects. More specifically, the invention is directed to the compositions and use of derivatized, *e.g.*, ester or carboxylic acid derivatized, antihistamine antagonists for the treatment of sleep disorders.

METHODS OF THE INVENTION

One embodiment of the invention is a method of treating a Central Nervous System (CNS) disorder. The method of treating comprises the treatment of a Central Nervous System (CNS) disorder, comprising administering to a subject an effective amount of a therapeutic compound, such that the therapeutic compound penetrates into the CNS and modulates the CNS target, thereby treating the CNS disorder.

The language "Central Nervous System (CNS) disorder,' includes disorders or states of the central nervous system and that are treatable by the compounds described herein. Examples include, but are not limited to depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis/disorder; depressive neurosis/disorder; anxiety neurosis; dysthymic disorder; behavior disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; sexual disorder; schizophrenia; manic depression; delirium; dementia; severe mental retardation and dyskinesias such as Huntington'' disease and Gilles de la Tourett's syndrome; disturbed biological and circadian rhythms; feeding disorders, such as anorexia, bulimia, cachexia, and obesity; diabetes; appetite/taste disorders; vomiting/nausea; asthma; cancer; Parkinson's disease; Cushing's syndrome / disease; basophil adenoma; prolactinoma; hyperprolactinemia; hypopituitarism; hypophysis tumor / adenoma; hypothalamic diseases; Froehlich's syndrome; adrenohypophysis disease; hypophysis tumor / adenoma; pituitary growth hormone; adrenohypophysis hypofunction; adrenohypophysis hyperfunction; hypothalamic hypogonadism; Kallman's syndrome (anosmia, hyposmia); functional or psychogenic amenorrhea; hypopituitarism; hypothalamic hypothyroidism; hypothalamic-adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth hormone deficiency; dwarfism; gigantism; acromegaly; disturbed biological and circadian rhythms; and sleep disturbances associated with such diseases as neurological disorders, neuropathic pain and restless leg syndrome, heart and lung diseases; acute and congestive heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardial infarction; ischaemic or haemorrhagic stroke; subarachnoid haemorrhage; head injury such as subarachnoid haemorrhage associated with traumatic head injury; ulcers; allergies; benign prostatic hypertrophy; chronic renal failure; renal disease; impaired glucose tolerance; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain, such as hyperalgesia, causalgia and allodynia; acute pain; burn pain; atypical facial

pain; neuropathic pain; back pain; complex regional pain syndromes I and II; arthritic pain; sports injury pain; pain related to infection, e.g., HIV, post-polio syndrome, and post-herpetic neuralgia; phantom limb pain; labor pain; cancer pain; post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; conditions associated with visceral pain including irritable bowel syndrome, migraine and angina; urinary bladder incontinence e.g. urge incontinence; tolerance to narcotics or withdrawal from narcotics; sleep disorders, sleep apnea; narcolepsy, insomnia; parasomnia; jet-lag syndrome; and neurodegenerative disorders, which include nosological entities such as disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-ponto-nigral degeneration, epilepsy and seizure disorders, attention-deficit hyperactivity disorder (ADHD)/cognition, Alzheimer's, drug abuse, stroke, multiple sclerosis (MS), and Amyotrophic Lateral Sclerosis (ALS).

The terms "treating" or "treatment" include administering a therapeutically effective amount of a compound sufficient to reduce or eliminate at least one symptom of the state, disease or disorder, *e.g.*, a sleep disorder.

The language "administering" includes delivery to a subject by any means that does not affect the ability of the therapeutic compound to perform its intended function. The therapeutic compound may be administered by any means that sufficiently treats the disorder target. Administration includes, but is not limited to parenteral, enteral, and topical administration. While it is possible for a compound of the present invention to be administered alone, it is preferable to administer the compound as a pharmaceutical composition, which includes compositions that comprise the compounds of the present invention and a pharmaceutically acceptable carrier. In a specific embodiment, the therapeutic compound is administered orally.

Administration also includes the use of an additional modulating factor (AMF) in "combination therapy." The language "additional modulating factor (AMF)" includes additional factors, such as additional therapeutics or subject abnormalities, *e.g.*, a chemical imbalance. It should be understood that the additional modulating factor may be directed to the same or a different disorder target as that being modulated by the compounds of the present invention. The language "combination therapy" includes the co-administration of the modulating compound of the present invention in the presence of an additional modulating factor, *e.g.*, an additional therapeutic agent. Administration of the modulating compound may be first, followed by the other therapeutic agent; or administration of the other therapeutic agent may be first, followed by the modulating, *e.g.*, inhibiting, compound. The other therapeutic agent may be any agent which is known in the art to treat, prevent, or reduce the symptoms of the targeted disorder, *e.g.*, a sleep disorder. In addition, the compounds of the present invention can also be administered in combination with other known therapies for the target disorder.

Furthermore, the other therapeutic agent may be any agent of benefit to the patient when administered in combination with the administration of a modulating, *e.g.*, inhibiting, compound. The other therapeutic agent may also be a modulating compound. For example, a therapeutic compound of the invention may be administered in conjunction with a variety of commercially-available drugs, including, but not limited to, antimicrobial agents, such as pentamidine, lomefloxacin, metronidazole, fungistatic agents, germicidal agents, hormones, antipyretic agents, antidiabetic agents, bronchodilators, such as aminophylline, antidiarrheal agents, such as diphenoxylate hydrochloride with atropine sulfate, antiarrhythmic agents, such as disopyramide phosphate and bidisomide, coronary dilation agents, glycosides, spasmolytics, antihypertensive agents, such as verapamil and verapamil hydrochloride and their enantiomers, and betaxolol, antidepressants, antianxiety agents, other psychotherapeutic agents, such as zolpidem, cycloserine and milacemide, corticosteroids, analgesics, such as misoprostol with diclofenac, contraceptives, such as ethynodiol diacetate with ethinyl estradiol, and norethynodrel with mestranol, nonsteroidal anti-inflammatory drugs, such as oxaprozen, blood glucose lowering agents, cholesterol lowering agents, anticonvulsant agents, other antiepileptic agents, immunomodulators, antioholinergics, sympatholytics, sympathomimetics, vasodilatory agents, anticoagulants, antiarrhythmics, such as disopyramide or disobutamide, prostaglandins having various pharmacologic activities, such as misoprostol and enisoprost, diuretics, such as spironolactone and spironolactone with hydrochlorothiazide, sleep aids, such as zolpidem tartrate, antihistaminic agents, antineoplastic agents, oncolytic agents, antiandrogens, antimalarial agents, antileprosy agents, and various other types of drugs. See Goodman and Gilman's The Basis of Therapeutics (Eighth Edition, Pergamon Press, Inc., USA, 1990) and The Merck Index (Eleventh Edition, Merck & Co., Inc., USA, 1989), each of which is incorporated herein by reference

In addition, a compound of the invention also may be administered in conjunction with any one or combination of the commercially-available, over-the-counter or prescription medications, including, but not limited to Avobenzene/padimate-O, ACCUPRIL® tablets (quinapril hydrochloride), Accutane capsules (isotretinoin), Achromycin V capsules (the monohydrochloride of (4S-(4.alpha., 4a.alpha.,5a.alpha.,6.beta., 12a.alpha.,))-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octBPydro-3,6,10,12,1 2a-pentBPydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide), Actifed cough syrup (codeine phosphate, triprolidine hydrochloride and pseudoephedrine hydrochloride), Aldactazide tablets (spironolactone and hydrochlorothiazide), ALDOCLOR® tablets (methyldopa and chlorothiazide), Aldoril tablets (methyldopa-hydrochlorothiazide), Alferon® N injection (interferon .alpha.-n3 (human leukocyte derived)), ALTACE™ capsules (ramipril), AMBIEN®

tablets (zolpidem tartrate), Anafranil capsules (clomipramine hydrochloride), ANAPROX® tablets (naproxen sodium), Ancobon capsules (flucytosine), Ansaid tablets (flurbiprofen), Apresazide capsules (hydralazine hydrochloride and hydrochlorothiazide), Asendin tablets (2-chloro-11-(1-piperazinyl)dibenz(b,f)(1,4)-oxazepine), Atretol™ tablets (carbamazepine), Aureomycin ophthalmic ointment (chlortetracycline hydrochloride), Azo Gantanol® tablets (sulfamethoxazole and phenazopyridine hydrochloride), Azo Gantrisin tablets (sulfisoxazole and phenazopyridine hydrochloride), Azulfidine® tablets and EN-tabs (5-((p-(2-pyridylsulfamoyl)phenyl)-azo)salicylic acid), Bactrim tablets (trimethoprim and sulfamethoxazole), Bactrim I.V. infusion (trimethoprim and sulfamethoxazole), Bactrim pediatric suspension (trimethoprim and sulfamethoxazole), Bactrim suspension (trimethoprim and sulfamethoxazole), Bactrim tablets (trimethoprim and sulfamethoxazole), Benadryl® capsules (diphenhydramine hydrochloride USP), Benadryl® kapseals (diphenhydramine hydrochloride USP), Benadryl® tablets (diphenhydramine hydrochloride USP), Benadryl® parenteral (diphenhydramine hydrochloride USP), Benadryl® steri-vials, ampoules, and steri-dose syringe (diphenhydramine hydrochloride USP), Capoten tablets (captopril), Capozide tablets (captopril-hydrochlorothiazide), Cardizem® CD capsules (diltiazem hydrochloride), Cardizem® SR capsules (diltiazem hydrochloride), Cardizem® tablets (diltiazem hydrochloride), Chibroxin sterile ophthalmic solution (with oral form) (norfloxacin), Children's Advil® suspension (ibuprofen), Cipro® I.V. (ciprofloxacin), Cipro® tablets (ciprofloxacin), Claritin tablets (loratadine), Clinoril tablets (sulindac), Combipres® tablets (clonidine hydrochloride and chlorthalidone), Compazine® injection (prochlorperazine maleate), Compazine® multi-dose vials (prochlorperazine maleate), Compazine® syringes (prochlorperazine maleate), Compazine® spansule capsules (prochlorperazine maleate), Compazine® suppositories (prochlorperazine maleate), Compazine® syrup (prochlorperazine maleate), Compazine® tablets (prochlorperazine maleate), Cordarone tablets (amiodarone hydrochloride), Corzide tablets (nadolol and bendroflumethiazide), Dantrium capsules (dantrolene sodium), Dapsone tablets (4-4' diaminodiphenylsulfone), DAYPRO® caplets (oxaproxin), Declomycin tablets (demeclacycline or (4S-(4.alpha.,4a.alpha.,5a.alpha.,6.beta.,12a.alpha.))-7-Chloro-4-dimethyl amino)-1,4,4a,5,5a,6,11,12a-octBPydro-3,6,10,12,12a-pentBPydroxy-1,11-dioxo -2-naphthacenecarboxamide monohydrochloride), DECONAMINE® capsules (chlorpheniramine maleate and d-psuedoephedrine hydrochloride), DECONAMINE® syrup (chlorpheniramine maleate and d-psudoephedrine hydrochloride), DECONAMINE® tablets (chlorpheniramine maleate and d-psudoephedrine hydrochloride), Depakene capsules (valproic acid), Depakene syrup (valproic acid), Depakote sprinkle capsules (divalproex sodium), Depakote tablets (divalproex sodium),

DiaBeta® tablets (glyburide), Diabinese tablets (chlorpropamide), Diamox parenteral (acetazolamide), Diamox sequels (acetazolamide), Diamox tablets (acetazolamide), Dimetane-DC cough syrup (brompheniramine maleate, phenylpropanolamine hydrochloride and codeine phosphate), Dimetane-DX cough syrup (brompheniramine maleate, phenylpropanolamine hydrochloride and codeine phosphate), Dipentum® capsules (olsalazine sodium), Diucardin tablets (hydroflumethiazide), Diupres tablets (reserpine and chlorothiazide), Diuril oral suspension (chlorothiazide), Diuril sodium intravenous (chlorothiazide), Diuril tablets (chlorothiazide), Dolobid tablets (diflunisal), DORYX® capsules (doxycycline hyclate), Dyazide capsules (hydrochlorothiazide and triamterene), Dyrenium capsules (triamterene), Efudex cream (5-fluorouracil), Efudex solutions (5-fluorouracil), Elavil injection (amitriptyline HCl), Elavil tablets (amitriptyline HCl), Eldepryl tablets (selegiline hydrochloride), Endep tablets (amitriptyline HCl), Enduron tablets (methyclothiazide), Enduronyl Forte tablets (methyclothiazide and deserpidine), Enduronyl tablets (methyclothiazide and deserpidine), Ergamisol tablets (levamisole hydrochloride), Esidrix tablets (hydrochlorothiazide USP), Esimil tablets (guanethidine monosulfate USP and hydrochlorothiazide USP), Etrafon Forte tablets (perphenazine, USP and amitriptyline hydrochloride, USP), Etrafon 2-10 tablets (perphenazine, USP and amitriptyline hydrochloride, USP), Etrafon tablets (perphenazine, USP and amitriptyline hydrochloride, USP), Etrafon-A tablets (perphenazine, USP and amitriptyline hydrochloride, USP), Eulexin capsules (flutamide), Exna tablets (benzthiazide), FUDR injection (floxuridine), Fansidar tablets (N1-(5,6-dimethoxy-4-pyrimidinyl) sulfanilamide (sulfadoxine) and 2,4-diamino-5-(p-chlorophenyl)-6-ethylpyrimidine (pyrimethamine), Feldene capsules (piroxicam), Flexeril tablets (cyclobenzaprine hydrochloride), FLOXIN® I.V. (ofloxacin injection), FLOXINS® tablets (ofloxacin), Fluorouracil injection (5-fluoro-2,4 (1H,3H)-pyrimidinedione), Fulvicin tablets (griseofulvin), Gantanol® suspension (sulfamethoxazole), Gantanol® tablets (sulfamethoxazole), Gantrisin ophthalmic ointment/solution (sulfisoxazole), Gantrisin pediatric suspension (sulfisoxazole), Gantrisin syrup (sulfisoxazole), Gantrisin tablets (sulfisoxazole), Glucotrol tablets (glipizide), Glynase PresTab tablets (glyburide), Grifulvin V tablets (griseofulvin), Grifulvin oral suspension (griseofulvin), Gristactin capsules (griseofulvin), Grisactin tablets (griseofulvin), Gris-PEG tablets (griseofulvin), Grivate tablets (griseofulvin), Grivate suspension (griseofulvin), Haldol Decanoate 50 injection (haloperidol decanoate), Haldol Decanoate 100 injection (haloperidol decanoate), Haldol tablets (haloperidol decanoate), Hibistat germicidal hand rinse (chlorhexidine gluconate), HISMANAL® tablets (astemizole), HydroDIURIL tablets (hydrochlorothiazide), Hydromox tablets (quinethazone), Hydropres tablets (reserpine and hydrochlorothiazide), Inderide® tablets (propranolol hydrochloride and

hydrochlorothiazide), Inderides capsule® (propranolol hydrochloride and hydrochlorothiazide), Intal inhaler (cromolyn sodium), Intron A injection (recombinant interferon .alpha.-2b), Lamprene capsules (clofazimine), Lasix oral solution (furosemide), Lasix tablets (furosemide), Lasix injection (furosemide), Limbitrol tablets (chlordiazepoxide and amitriptyline hydrochloride), Lodine capsules (etodolac), Lopressor HCT tablets (metoprolol tartrate USP and hydrochlorothiazide USP), Lotensin tablets (benazepril hydrochloride), LOZOL® tablets (indapamide), Ludiomil tablets (maprotiline hydrochloride USP), Marplan tablets (isocarboxazid), MAXAQUIN® tablets (lomefloxacin HCl), Maxzide tablets (triamterene USP and hydrochlorothiazide USP), Mellaril® concentrate (thioridazine), Mellaril® tablets (thioridazine), Mellaril-S suspension (thioridazine), Mepergan injection (meperidine hydrochloride and promethazine hydrochloride), Methotrexate tablets (methotrexate), Mevacor tablets (lovastatin), Micronase tablets (glyburide), Minizide capsules (prazosin hydrochloride and polythiazide), Minocin intravenous ((4S-(4.alpha.,4a.alpha.,5a.alpha.,12a.alpha.))-4,7-bis(dimethylamino)-1,4 ,4a,5,5a,6,11,12a-octBPydro-3,10,12,12a-tetrBPydroxy-1,11-dioxo-2-naphthace necarboxamide monohydrochloride), Minocin oral suspension ((4S-(4.alpha., 4a.alpha.,5a.alpha.,12a.alpha.))-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,1 2a-octBPydro-3,10,12,12a-tetrBPydroxy-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride), Minocin capsules ((4S-(4.alpha.,4a.alpha.,5a.alpha.,12a.alpha.))-4,7-bis(dimethylamino)-1,4 ,4a,5,5a,6,11,12a-octBPydro-3,10,12,12a-tetrBPydroxy-1,11-dioxo-2-naphthace necarboxamide monohydrochloride), Moduretic tablets (amiloride HCl-hydrochlorothiazide), Monodox® capsules (doxycycline monohydrate), Monopril tablets (fosinopril sodium), Children's Motrin liquid suspension (ibuprofen), Motrin tablets (ibuprofen), Mykrox tablets (metolazone), NAPROSYN® suspension (naproxen), NAPROSYN® tablets (naproxen), Navane capsules (thiothixene), Navane intramuscular (thiothixene), NegGram caplets (nalidixic acid), NegGram suspension (nalidixic acid), Neptazane tablets (methazolamide), Nipent injection (pentostatin), Normodyne tablets (labetalol HCl), NOROXIN tablets (norfloxacin), Norpramin tablets (desipramine hydrochloride USP), oretic tablets (hydrochlorothiazide), Oreticyl Forte tablets (hydrochlorothiazide and deserpidine), Orinase tablets (tolbutamide), Ornade capsules (phenylpropanolamine hydrochloride and chlorpheniramine maleate), Orudis capsules (ketoprofen), Oxsoralen lotion (methoxypsoralen), PBZ tablets (tripelennamine hydrochloride USP), PBZ-SR tablets (tripelennamine hydrochloride USP), pHisoHex topical emulsion (hexachlorophene), P & S PLUS® topical tar gel (crude coal tar), Pamelor® capsules (nortriptyline HCl), Pamelor® solution (nortriptyline HCl), Paxil tablets (paroxetine hydrochloride), Pediazole oral suspension (erythromycin ethylsuccinate, USP and sulfisoxazole acetyl, USP), Penetrex.TM. tablets (enoxacin), Pentasa capsules

(mesalamine), Periactin syrup (cyproheptadine HCl), Periactin tablets (cyproheptadine HCl), Phenergan tablets (promethazine hydrochloride), Phenergan injection (promethazine hydrochloride), Phenergan suppositories (promethazine hydrochloride), Phenergan syrup (promethazine hydrochloride), Polytrim® ophthalmic solution (trimethoprim sulfate and polymyxin B sulfate), Pravachol (pravastatin sodium), Prinivil® tablets (lisinopril, MSD), Prinzide tablets (lisinopril-hydrochlorothiazide), Prolixin elixir (fluphenazine hydrochloride), Prolixin enanthate (fluphenazine hydrochloride), Prolixin injection (fluphenazine hydrochloride), Prolixin oral concentrate (fluphenazine hydrochloride), Prolixin tablets (fluphenazine hydrochloride), ProSom tablets (estazolam), Prozac® oral solution (fluoxetine hydrochloride), Prozac® oral Pulvules® (fluoxetine hydrochloride), Pyrazinamide tablets (pyrazinamide), QUINAGLUTE® tablets (quinidine gluconate), Quinidex tablets (quinidine sulfate), Relafen tablets (nabumetone), Ru-Tuss II capsules (chlorpheniramine maleate and phenylpropanolamine hydrochloride), Seldane tablets (terfenadine), Septra tablets (trimethoprim and sulfamethoxazole), Septra suspension (trimethoprim and sulfamethoxazole), Septra I.V. infusion (trimethoprim and sulfamethoxazole), Septra tablets (trimethoprim and sulfamethoxazole), Ser-Ap-Es tablets (reserpine USP, hydralazine hydrochloride USP and hydrochlorothiazide USP), Sinequan capsules (doxepin HCl), Solganal injection (aurothioglucose, USP), Stelazine concentrate (trifluoperazine hydrochloride), Stelazine injection (trifluoperazine hydrochloride), Stelazine tablets (trifluoperazine hydrochloride), Surmontil capsules (trimipramine maleate), SYMMETREL capsules and syrup (amantadine hydrochloride), Taractan concentrate (chlorprothixene), Taractan injectable (chlorprothixene), Taractan tablets (chlorprothixene), TAVIST® syrup (clemastine fumarate, USP), TAVIST® tablets (clemastine fumarate, USP), TAVIST®-1 12 hour relief medicine (clemastine fumarate, USP), TAVIST®-D 12 hour relief medicine (clemastine fumarate, USP), Tegretol Tablets (carbamazepine USP), Tegretol suspension (carbamazepine USP), Temaril tablets (trimeprazine tartrate), Temaril syrup (trimeprazine tartrate), Temaril capsules (trimeprazine tartrate), TENORETIC® tablets (atenolol and chlorthalidone), Terramycin intramuscular solution (oxytetracycline), Thiosulfil Forte tablets (sulfamethizole), Thorazine ampuls (chlorpromazine hydrochloride), Thorazine concentrate (chlorpromazine hydrochloride), Thorazine multi-dose vials (chlorpromazine hydrochloride), Thorazine capsules (chlorpromazine hydrochloride), Thorazine suppositories (chlorpromazine hydrochloride), Thorazine syrup (chlorpromazine hydrochloride), Thorazine tablets (chlorpromazine hydrochloride), Timolide tablets (timolol maleate-hydrochlorothiazide), Tofranil ampuls (imipramine hydrochloride USP), Tofranil tablets (imipramine hydrochloride USP), Tofranil capsules (imipramine hydrochloride USP), Tolinase tablets (tolazamide), Triaminic Expectorant DH

(phenylpropanolamine hydrochloride and guaifenesin), Triaminic oral infant drops (phenylpropanolamine hydrochloride, pheniramine maleate and pyrilamine maleate), Triavil tablets (perphenazine-amitriptyline HCl), Trilafon concentrate (perphenazine USP), Trilafon injection (perphenazine USP), Trilafon tablets (perphenazine, USP), Trinalin tablets (azatadine maleate, USP, and pseudoephedrine sulfate, USP), Vaseretic tablets (enalapril maleate-hydrochlorothiazide), Vasosulf opthalmic solution (sulfacetamide sodium-phenylephrine hydrochloride), Vasotec I.V. (enalapril maleate), Vasotec tablets (enalapril maleate), Velban® vials (vinblastine sulfate, USP), Vibramycin capsules (doxycycline monohydrate), Vibramycin intravenous (doxycycline monohydrate), Vibramycin oral suspension (doxycycline monohydrate), Vibra-Tabs tablets (oxytetracycline), Vivactil tablets (protriptyline HCl), Voltaren tablets (diclofenac sodium), X-SEB T® shampoo (crude coal tar), Zaroxolyn tablets (metolazone), ZESTORETIC® oral (lisinopril and hydrochlorothiazide), ZESTRIL® tablets (lisinopril), ZITHROMAX™ capsules (azithromycin), Zocor tablets (simvastatin), ZOLOFT® tablets (sertraline hydrochloride) and others.

A compound of the invention may also be administered in conjunction with the use of physical methods such as with light therapy or electrical stimulation.

The term "pharmaceutically acceptable carrier" include a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting a compound(s) of the present invention within or to the subject such that it can perform its intended function. Typically, such compounds are carried or transported from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical formulations.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents,

sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically acceptable antioxidants include: water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Formulations of the present invention include those suitable for oral, nasal, topical, transdermal, buccal, sublingual, rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 1 percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; binders, such as, for example,

carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; humectants, such as glycerol; disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; solution retarding agents, such as paraffin; absorption accelerators, such as quaternary ammonium compounds; wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; absorbents, such as kaolin and bentonite clay; lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and coloring agents. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms for oral administration of the compounds of the invention include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may

contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by

dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the active compound in a polymer matrix or gel.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer

employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

The preparations of the present invention may be given orally, parenterally, topically, or rectally. They are of course given by forms suitable for each administration route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, etc. administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories. Oral administration is preferred.

The terms "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

The terms "systemic administration," "administered systematically," "peripheral administration" and "administered peripherally" as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, for example, subcutaneous administration, such that it enters the patient's system and thus, is possibly subject to metabolism and other like processes.

These compounds may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually.

Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age,

sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

The regimen of administration can affect what constitutes an effective amount. The disorder target modulators, *e.g.*, CNS disorder target modulators, can be administered to the subject either prior to or after the onset of a CNS disorder associated state. Further, several divided dosages, as well as staggered dosages, can be administered daily or sequentially, or the dose can be continuously infused, or can be a bolus injection. Further, the dosages of the disorder target modulators, *e.g.*, CNS disorder target modulators, compound(s) can be proportionally increased or decreased as indicated by the exigencies of the therapeutic or prophylactic situation.

The language "subject" includes animals (*e.g.*, mammals, *e.g.*, cats, dogs, horses, pigs, cows, sheep, rodents, rabbits, squirrels, bears, primates (*e.g.*, chimpanzees, gorillas, and humans) which are capable of suffering from a CNS associated disorder, e.g., a sleep disorder.

The language "therapeutically effective amount" of the compound is that amount necessary or sufficient to treat or prevent a state associated with a disorder, *e.g.*, CNS disorder. The effective amount can vary depending on such factors as the size and weight of the subject, the type of illness, or the particular compound. For example, the choice of the therapeutic compound can affect what constitutes an "effective amount". One of ordinary skill in the art would be able to study the aforementioned factors and make the determination regarding the effective amount of the therapeutic compound without undue experimentation.

The language "penetrates into the CNS" includes the favorable biological property of a compound of the current invention to pass though, or penetrate, the blood brain barrier (BBB) and enter into the CNS.

The language "therapeutic compound" includes compounds of the invention capable of performing their intended function, *e.g.*, treating CNS disorders and/or modulating CNS targets. The therapeutic compounds of the invention are described in detail herein.

Accordingly, the therapeutic compound can have the formula:

$[CA]-(SP)_n-[DA]$

wherein CA includes moieties that modulate an active CNS target receptor or a collection of active CNS target receptors.

The language "drug activity modulating moiety", or "DA" is a moiety that provides the ability to modulate the activity of the therapeutic compound. Examples include functional moieties, *e.g.*, ester, carboxylic acid or alcohol groups, selected and positioned within the therapeutic drug to provide the ability to modulate the activity of the drug, *e.g.*, modulate, *e.g.*, increase, the half-life of the drug, the ability of the drug to cross the blood brain barrier, or the ability of the drug to bind selectively to the desired receptor. In certain embodiments of the invention, the drug activity modulating moiety is an ester group, EG. In particular embodiments, the activity of the drug, *e.g.*, half-life, of the therapeutic drug is modulated by controlling the rate of hydrolysis of the ester group by selection and positioning of steric bulk near the ester carbonyl of the ester group. In certain embodiments, the steric bulk is provided by the selection of a bulky ester group. In alternative embodiments the steric bulk is provided by substitution selected and positioned on the CA moiety, *e.g.*, an AH moiety, near the carbonyl of the ester group.

In a specific embodiment, the drug activity modulating moiety is a carboxylic acid. In certain embodiments of the invention, the presence of the carboxylic acid results in increased concentration of the therapeutic compound within the CNS for a discrete period of time as a result of the existence of an ionic bond that includes the carboxylate ion of the corresponding carboxylic acid, *e.g.*, zwitterion species formation with a nitrogen atom within the compound or salt bridge formation. In one embodiment, penetration through the blood brain barrier into the CNS results from the lipophilicity of substituents or conformational lipophilicity, *i.e.*, lipophilicity as a result of a particular conformation, such as internal salt formation between a carboxylate anion and a protonated amine. In another embodiment, the presence of the carboxylic acid improves the ability of the compound to bind selectively to the desired receptor.

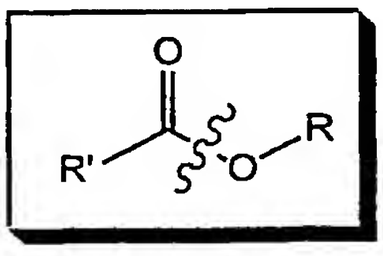
The language "ester group" includes an organic ester functionality that is selected and positioned within the compound providing the ability to modulate the activity or modify the properties of the corresponding therapeutic compound. The organic ester group may be terminal, *e.g.*, a substituent, or internal. The carboxylate of

the ester may be oriented from left to right or from right to left, *e.g.*, a reverse ester. Examples of esters of the current invention include, but are not limited to hydrocarbons and perfluorocarbons. In a preferred embodiment, the hydrocarbons posses 1 to 20 carbons. In certain embodiments, the hydrocarbons can be linear, branched, cyclic, aromatic, and a combination of aliphatic and aromatic, which are optionally substituted with O, N, S, and/or halogens and may additionally include a center of chirality. In particular embodiments, the ester can be an n-propyl, an isopropyl, a t-butyl, a cyclopentyl, a cyclohexyl, a cycloheptyl, and a benzyl group.

The language "bulky ester" is intended to include an ester that has sufficient steric properties such that the rate of hydrolysis of the therapeutic compound is modulated, *e.g.*, reduced, such that the activity of the therapeutic compound is modified, *e.g.*, the length of activity is increased (*i.e.*, the half-life of the therapeutic compound is increased). Examples of bulky ester groups are depicted in Table 1.

Table 1

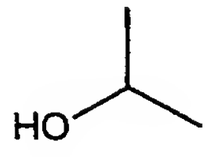
Bulky Groups For H1 Antagonist Esters

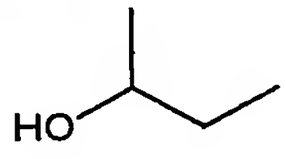


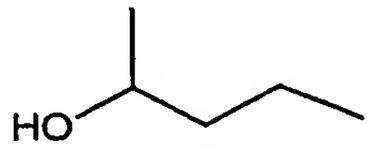
R' = Parent Drug Core Structure

R = Ester from Alcohols below

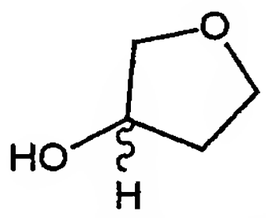
TYPE A:



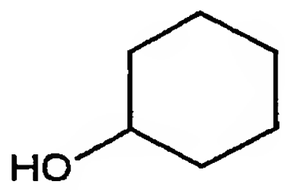




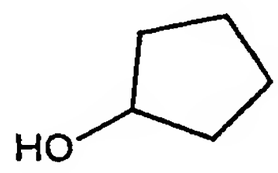
TYPE B:

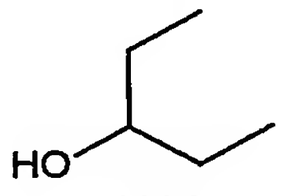


Aldrich as R,S mixture
and pure R or S enantiomers.
Prepare esters with R,S mixture first.

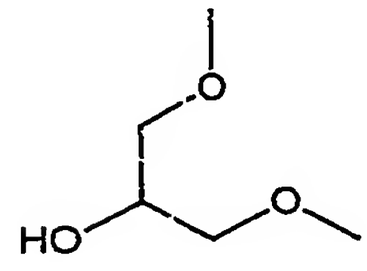


Aldrich

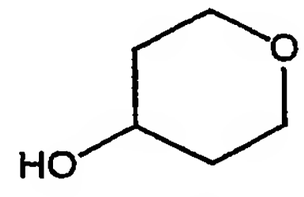




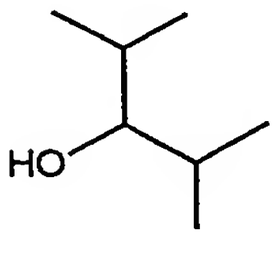
Aldrich



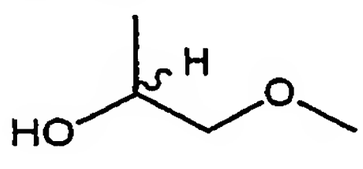
1,3-dimethoxy-2-propanol
Tyger Scientific Inc.
Ewing, NJ



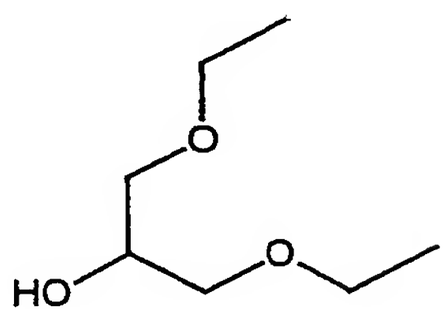
Aldrich



Aldrich



Aldrich as R,S mixture
Acros as pure R or S enantiomers.
Prepare esters with R,S mixture first.



Lancaster or TCI

Aldrich

In certain embodiments, the ester is not methyl, ethyl, or n-propyl. In certain embodiments of the invention, the bulky ester is not an n-propyl, isopropyl, n-butyl, isobutyl, or tert-butyl ester. In certain embodiments of the invention, the ester is not a C-1 to C-4 ester. In certain embodiments of the invention wherein the therapeutic

compound is a diphenhydramine-like, triprolidine-like, and doxepin-like compound, the ester is not a C-1 to C-4 ester and/or a C-3 to C-4 bulky ester.

The language "hydrocarbon" as used herein, includes substituted or unsubstituted alkyl, alkenyl, alkynyl, and aromatic or aryl moieties. The term "alkyl" includes saturated aliphatic groups, including straight-chain alkyl groups (e.g., methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, etc.), branched-chain alkyl groups (isopropyl, tert-butyl, isobutyl, etc.), cycloalkyl (alicyclic) groups (cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl), alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. The term alkyl further includes alkyl groups, which can further include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkyl has 6 or fewer carbon atoms in its backbone (e.g., C_1-C_6 for straight chain, C_3-C_6 for branched chain), and more preferably 4 or fewer. Likewise, preferred cycloalkyls have from 3-8 carbon atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure. The term C_1-C_6 includes alkyl groups containing 1 to 6 carbon atoms.

Moreover, the term alkyl includes both "unsubstituted alkyls" and "substituted alkyls", the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Cycloalkyls can be further substituted, e.g., with the substituents described above. An "alkylaryl" or an "aralkyl" moiety is an alkyl substituted with an aryl (e.g., phenylmethyl (benzyl)). The term "alkyl" also includes the side chains of natural and unnatural amino acids.

The term "aryl" includes groups, including 5- and 6-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, phenyl, pyrrole, furan, thiophene, thiazole, isothiaozole, imidazole, triazole, tetrazole, pyrazole, oxazole, isooxazole, pyridine, pyrazine, pyridazine, and pyrimidine, and the like. Furthermore, the term "aryl" includes multicyclic aryl groups, e.g., tricyclic, bicyclic, e.g., naphthalene, benzoxazole, benzodioxazole, benzothiazole, benzoimidazole, benzothiophene, methylenedioxyphenyl, quinoline, isoquinoline,

napthridine, indole, benzofuran, purine, benzofuran, deazapurine, or indolizine. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles", "heterocycles," "heteroaryls" or "heteroaromatics". The aromatic ring can be substituted at one or more ring positions with such substituents as described above, as for example, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkylaminoacarbonyl, aralkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl groups can also be fused or bridged with alicyclic or heterocyclic rings which are not aromatic so as to form a polycycle (e.g., tetralin).

The term "alkenyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond.

For example, the term "alkenyl" includes straight-chain alkenyl groups (e.g., ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, etc.), branched-chain alkenyl groups, cycloalkenyl (alicyclic) groups (cyclopropenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl), alkyl or alkenyl substituted cycloalkenyl groups, and cycloalkyl or cycloalkenyl substituted alkenyl groups. The term alkenyl further includes alkenyl groups which include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkenyl group has 6 or fewer carbon atoms in its backbone (e.g., C_2-C_6 for straight chain, C_3-C_6 for branched chain). Likewise, cycloalkenyl groups may have from 3-8 carbon atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure. The term C_2-C_6 includes alkenyl groups containing 2 to 6 carbon atoms.

Moreover, the term alkenyl includes both "unsubstituted alkenyls" and "substituted alkenyls", the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate,

phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "alkynyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond.

For example, the term "alkynyl" includes straight-chain alkynyl groups (e.g., ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, etc.), branched-chain alkynyl groups, and cycloalkyl or cycloalkenyl substituted alkynyl groups. The term alkynyl further includes alkynyl groups which include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkynyl group has 6 or fewer carbon atoms in its backbone (e.g., C_2-C_6 for straight chain, C_3-C_6 for branched chain). The term C_2-C_6 includes alkynyl groups containing 2 to 6 carbon atoms.

Moreover, the term alkynyl includes both "unsubstituted alkynyls" and "substituted alkynyls", the latter of which refers to alkynyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

Unless the number of carbons is otherwise specified, "lower alkyl" as used herein means an alkyl group, as defined above, but having from one to five carbon atoms in its backbone structure. "Lower alkenyl" and "lower alkynyl" have chain lengths of, for example, 2-5 carbon atoms.

The term “acyl” includes compounds and moieties that contain the acyl radical (CH_3CO-) or a carbonyl group. The term “substituted acyl” includes acyl groups where one or more of the hydrogen atoms are replaced by for example, alkyl groups, alkynyl

groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "acylamino" includes moieties wherein an acyl moiety is bonded to an amino group. For example, the term includes alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido groups.

The term "aroyl" includes compounds and moieties with an aryl or heteroaromatic moiety bound to a carbonyl group. Examples of aroyl groups include phenylcarboxy, naphthyl carboxy, etc.

The terms "alkoxyalkyl", "alkylaminoalkyl" and "thioalkoxyalkyl" include alkyl groups, as described above, which further include oxygen, nitrogen or sulfur atoms replacing one or more carbons of the hydrocarbon backbone, e.g., oxygen, nitrogen or sulfur atoms.

The term "alkoxy" includes substituted and unsubstituted alkyl, alkenyl, and alkynyl groups covalently linked to an oxygen atom. Examples of alkoxy groups include methoxy, ethoxy, isopropyloxy, propoxy, butoxy, and pentoxy groups. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy, trichloromethoxy, etc.

The term "amine" or "amino" includes compounds where a nitrogen atom is covalently bonded to at least one carbon or heteroatom. The term "alkyl amino" includes groups and compounds wherein the nitrogen is bound to at least one additional

alkyl group. The term "dialkyl amino" includes groups wherein the nitrogen atom is bound to at least two additional alkyl groups. The term "arylamino" and "diarylamino" include groups wherein the nitrogen is bound to at least one or two aryl groups, respectively. The term "alkylarylamino," "alkylaminoaryl" or "arylaminoalkyl" refers to an amino group that is bound to at least one alkyl group and at least one aryl group. The term "alkaminoalkyl" refers to an alkyl, alkenyl, or alkynyl group bound to a nitrogen atom that is also bound to an alkyl group.

The term "amide" or "aminocarboxy" includes compounds or moieties that contain a nitrogen atom that is bound to the carbon of a carbonyl or a thiocarbonyl group. The term includes "alkaminocarboxy" groups that include alkyl, alkenyl, or alkynyl groups bound to an amino group bound to a carboxy group. It includes arylaminocarboxy groups that include aryl or heteroaryl moieties bound to an amino group that is bound to the carbon of a carbonyl or thiocarbonyl group. The terms "alkylaminocarboxy," "alkenylaminocarboxy," "alkynylaminocarboxy," and "arylaminocarboxy" include moieties wherein alkyl, alkenyl, alkynyl and aryl moieties, respectively, are bound to a nitrogen atom which is in turn bound to the carbon of a carbonyl group.

The term "carbonyl" or "carboxy" includes compounds and moieties that contain a carbon connected with a double bond to an oxygen atom. Examples of moieties that contain a carbonyl include aldehydes, ketones, carboxylic acids, amides, esters, anhydrides, etc.

The term "thiocarbonyl" or "thiocarboxy" includes compounds and moieties that contain a carbon connected with a double bond to a sulfur atom.

The term "ether" includes compounds or moieties that contain an oxygen bonded to two different carbon atoms or heteroatoms. For example, the term includes "alkoxyalkyl" which refers to an alkyl, alkenyl, or alkynyl group covalently bonded to an oxygen atom which is covalently bonded to another alkyl group.

The term "thioether" includes compounds and moieties that contain a sulfur atom bonded to two different carbon or hetero atoms. Examples of thioethers include, but are not limited to alkthioalkyls, alkthioalkenyls, and alkthioalkynyls. The term "alkthioalkyls" include compounds with an alkyl, alkenyl, or alkynyl group bonded to a sulfur atom that is bonded to an alkyl group. Similarly, the term "alkthioalkenyls" and alkthioalkynyls" refer to compounds or moieties wherein an alkyl, alkenyl, or alkynyl group is bonded to a sulfur atom that is covalently bonded to an alkynyl group.

The term "hydroxy" or "hydroxyl" includes groups with an –OH or $-O^-$.

The term "halogen" includes fluorine, bromine, chlorine, iodine, etc. The term "perhalogenated," *e.g.*, perfluorinated, generally refers to a moiety, *e.g.*, perfluorocarbons, wherein all hydrogens are replaced by halogen atoms, *e.g.*, fluorine.

The terms "polycyclyl" or "polycyclic radical" refer to two or more cyclic rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in which two or more carbons are common to two adjoining rings, e.g., the rings are "fused rings". Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycycle can be substituted with such substituents as described above, as for example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, alkylaminoacarbonyl, aralkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, alkenylcarbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "heteroatom" includes atoms of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, sulfur and phosphorus.

In certain embodiments, the ester group does not substantially effect the biological activity of the therapeutic compound. Alternatively, in certain other embodiments the ester group significantly effects the biological activity of the therapeutic compound. In one embodiment of the invention, the ester group improves the biological activity of the therapeutic compound.

When the ester is a methyl or an ethyl ester, the formulation of the therapeutic compound is formulated to sufficiently treat the target disorder. In addition, formulations of the therapeutic compound can be used to provide controlled *in vivo* adsorption of the therapeutic compound over a discrete period of time.

In certain embodiments of the invention, the compound containing the drug activity modulating group, *e.g.*, an ester, carboxylic acid, or alcohol group, possesses an improved selectivity of the drug for a desired receptor versus an undesired receptors over the corresponding compound without this group. In certain embodiments of the invention, the compound containing the drug activity modulating group, *e.g.*, an ester, carboxylic acid, or alcohol group, is more active as a therapeutic agent for treating disorders than the corresponding compound without this group. In specific embodiments, the ester is more active as a therapeutic agent for treating disorders than the corresponding acid of the ester. In particular embodiments, the corresponding acid of the ester is not a therapeutically active agent for treating disorders. In alternative embodiments, the corresponding acid of an ester is more active as a therapeutic agent for treating disorders than the corresponding ester of the acid. In a particular embodiment,

the carboxylic acid drug activity modulating group provides an internal salt with an amine and facilitates crossing the blood brain barrier.

One skilled in the art would recognize that the ester groups, as described above, could be extended to thioesters. Labile amides may also be used in replacement of the ester group, wherein the *in vivo* hydrolysis would be performed by peptidases in the CNS.

The language "biological activity" includes activity associated with the intended biological function of the compounds of the present invention, *e.g.*, treating a CNS disorder.

The language "modulate a target" or "modulation of a target" includes the act of agonizing or antagonizing a receptor or group of receptors of a target disorder. Thus, a compound that agonizes or antagonizes a receptor or group of receptors is referred to herein as a target modulator, *e.g.*, CNS disorder target modulator. The language "target modulator" includes compounds or compositions, *e.g.*, pharmaceutical compositions, which are used to modulate a target, *e.g.*, a CNS disorder target, *e.g.*, a sleep disorder target

The terms "modification" or "modifies" include controlling or adjusting physical or chemical parameters, *e.g.*, the half-life, of the therapeutic compound *in vivo* by changing one or more factors, *e.g.*, the lipophilicity, electronic properties and/or steric size of the drug activity modulating moiety, *e.g.*, ester group.

The language "spacer molecule" or "SP" includes molecules or moieties that are positioned within the compound to allow the compound to perform its intended function. In certain embodiments, the spacer molecule may be present. Alternatively, in certain other embodiments, the spacer molecule may not be present. In certain embodiments, the spacer molecule may be $(CH_2)_m$, where m is an integer number selected from 1 to 20. In addition, the spacer molecule, *e.g.*, the $(CH_2)_m$ linker to an ester or a carboxylic acid group, can be substituted with one or more substituents. In one embodiment, the spacer molecule is mono-substituted. In another embodiment of the invention, the spacer molecule is disubstituted. In particular embodiments, the linkers of the invention may be geminally-dialkylated, *e.g.*, gem-dimethylated, singly substituted with a substituent other than a noncyclic alkyl group, *e.g.*, a heteroatom, or a cyclic substituent wherein one or more of the carbons of the spacer molecule is contained in the ring, *e.g.*, heterocycle (*e.g.*, tetrahydropyran or tetrahydrofuran), or cyclic alkyl, *e.g.*, cyclopropyl. However, the substitution of the spacer molecule is independent of the substitution elsewhere in the molecule.

The term "target" includes a receptor or group of receptors that have been identified as useful point of action for a therapeutic compound, *e.g.*, CNS target, *e.g.*, sleep disorder target, *e.g.*, histamine receptor.

The language "receptor" includes specific sites of binding or action within a subject, associated or responsible for the activity of the target disorder, *e.g.*, a histamine or adenosine receptor.

The language "group of receptors" includes two or more receptors that may comprise the same receptor type or may comprise two or more receptor types.

In particular, the therapeutic compound of the invention may comprise the formula:

$$[CA]\text{-}(SP)_n\text{-}[EG]$$

wherein CA is a compound that modulates an active CNS target receptor or a collection of active CNS target receptors, EG is an ester group that modifies the half-life of the therapeutic compound, SP is a spacer molecule, and n is 0 or 1.

In certain embodiments, the CNS disorder is a sleep disorder. In particular embodiments of the current invention wherein the CNS disorder is a sleep disorder, the therapeutic compound of the invention may comprise one of the formulae:

$$[AD]\text{-}(SP)_n\text{-}[EG]$$

$$[AH]\text{-}(SP)_n\text{-}[DA], \text{ or}$$

$$[AH]\text{-}(SP)_n\text{-}[EG]$$

wherein AH is a compound that antagonizes a histamine receptor or a collection of histamine receptors, AD is a compound that agonizes an adenosine receptor or a collection of adenosine receptors, DA is a drug activity modulating moiety that provides the ability to modulate the activity of the therapeutic compound, EG is an ester group that modifies the half-life of the therapeutic compound, SP is a spacer molecule, and n is 0 or 1.

The language "compounds that agonize" a receptor, *e.g.*, agonizes an adenosine receptor, are intended to include compounds that induce the activity of the receptor and agents that up-regulate (*i.e.*, induce) the synthesis or production of the receptor.

The language "compounds that antagonize" a receptor, *e.g.*, a histamine receptor, are intended to include compounds that inhibit the activity of the receptor and agents that down-regulate (*i.e.*, inhibit) the synthesis or production of the receptor.

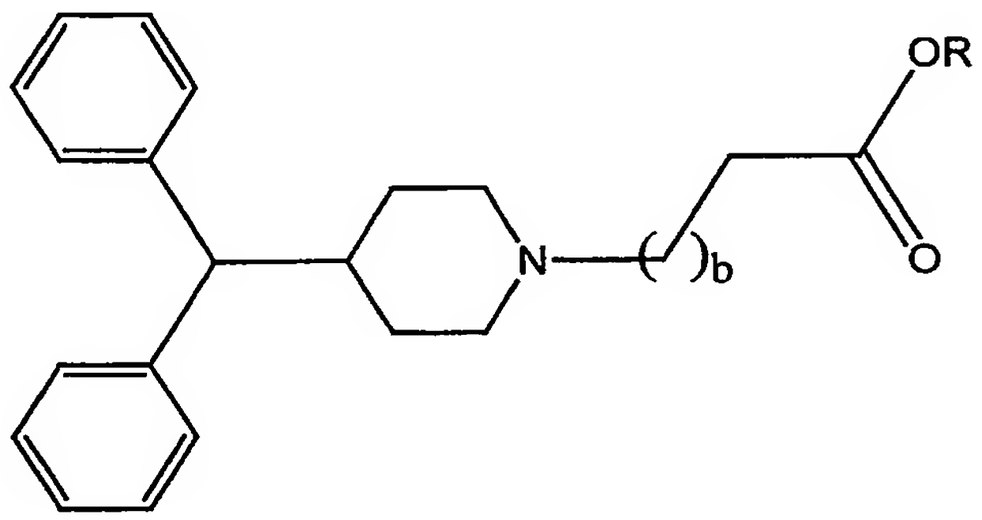
The language "adenosine receptor agonist" is intended to include art recognized allosteric and nonallosteric adenosine receptor agonists, including, but not limited to cyclohexyladenosine, pentostatin, conformycin, and purine and adenyl derivatives that

useful as adenosine precursors for the enhancement of adenosine synthesis. Adenosine has been reported to have cardioprotective and neuroprotective properties. It is reportedly released from cells in response to alterations in the supply of or demand for oxygen, is said to be a potent vasodilator, and is believed to be involved in the metabolic regulation of blood flow. However, adenosine has a short half-life (<1 sec) in human blood, and therefore high doses of adenosine would need to be administered continuously to achieve effective levels. However, high doses of adenosine have been reported to be toxic, and thus limit its therapeutic potential. It is also believed that by increasing adenosine concentration locally, *i.e.*, at the target site within the target tissue, the beneficial effects of adenosine can be provided and the toxic systemic effects minimized. In certain embodiments of the invention, the therapeutic compounds of formula [AD]-$(SP)_n$-[EG], described above, may be used in the methods of the current invention to increase the local adenosine concentration.

The language "histamine antagonist," "antihistamine" and "[AH]" are used interchangeably and are intended to include any compound that antagonizes a histamine or group of histamine receptors. In certain embodiments, the compound of the invention will bind to a histamine receptor with an affinity of less than about 100 μM, *e.g.*, less than about 10 μM. In one embodiment, antihistamines of the present invention contain at least two aryl rings that are separated by about 2-5 atoms from a basic nitrogen atom. In specific embodiments, the two aryl rings are connected to the same atom. The language "histamine antagonist" is intended to include art-recognized antihistamines, including both first and second generation antihistamines. For example, the antihistamines of the invention include, but are not limited to, antihistamines such as ethylenediamines, ethanolamines, alkylamines, phenothiazines, piperazines, piperdines, ketotifen, ebastine, terfenadine, acrivastine, triprolidine, doxepin, amitriptyline, trimipramine, protriptyline, nortriptyline, desipramine, pheniramine, diphenhydramine, mequitazine, cyproheptadine, clemastine, diphenylpyraline, promethazine, homochlorocyclizine, alimemazine, mepyramine, methapyraline, peroxatine, trazodone, nefazodone, hydroxyzine, meclizine loratidine, azelastine, levocabastine, cetirizine, fexofenadine, mizolastine, mirtazapine, and astemizole.

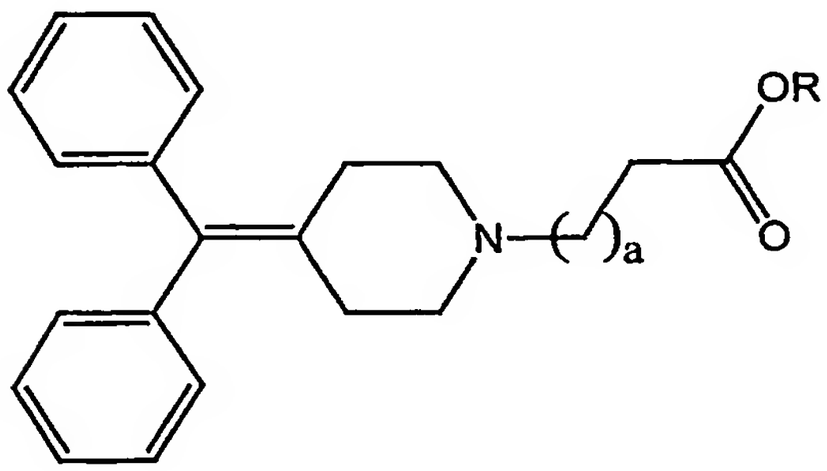
Classes of antihistamines of the instant invention also include pheniramine-like compounds, doxepin-like compounds, diphenhydramine-like compounds, triprolidine-like compounds, pheniramine analogs, and acrivastine analogs (see for example, Tables 2 and 3). It should be understood that the classes of antihistamines can be substituted or unsubstituted. In addition, the substituent(s) is selected and positioned within the molecule such that the compound is able to perform its intended function. Specific examples and locations of the substituents are discussed below.

The language "pheniramine-like compounds" is intended to include antihistamines that include two aryl groups linked to the same atom, not linked through a tricyclic ring system. In addition, pheniramine-like compounds are distinguished from diphenhydramine-like compounds by the lack of an oxygen atom linking the carbon atom, which is attached to the aryl groups, to a piperidine ring. In certain embodiments, the pheniramine-like compounds are represented by Formula (I) and Formula (II):



(I)

And

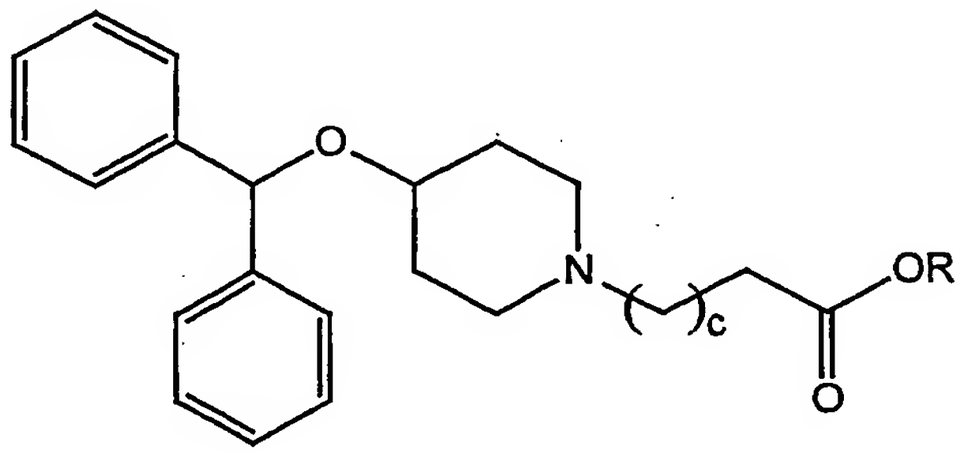


(II)

wherein a = 0 through 5, b = 0 through 5, and R is H or any group which imparts properties to the therapeutic compound to promote penetration into the CNS and to modify the half-life of the compound.

The language "diphenhydramine-like compounds" is intended to include antihistamines that include two aryl groups linked to the same atom, not linked through a tricyclic ring system, and are distinguished by the presence of an oxygen atom linking

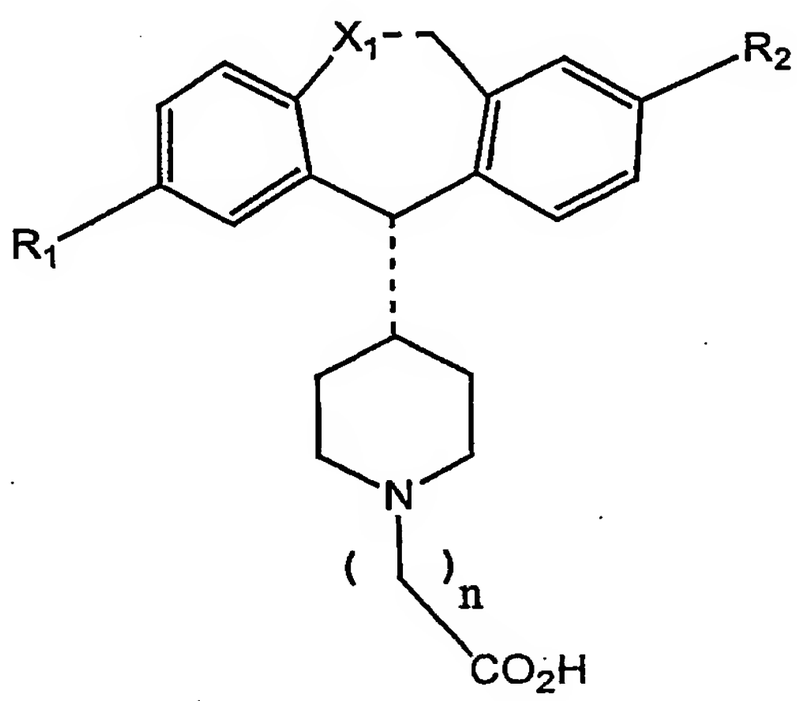
the carbon atom, which is attached to the aryl groups, to a piperidine ring. In certain embodiments, the diphenhydramine-like compounds are represented by Formula (III):



(III)

wherein c = 0 through 5, and R is H or any group which imparts properties to the therapeutic compound to promote penetration into the CNS and to modify the half-life of the compound.

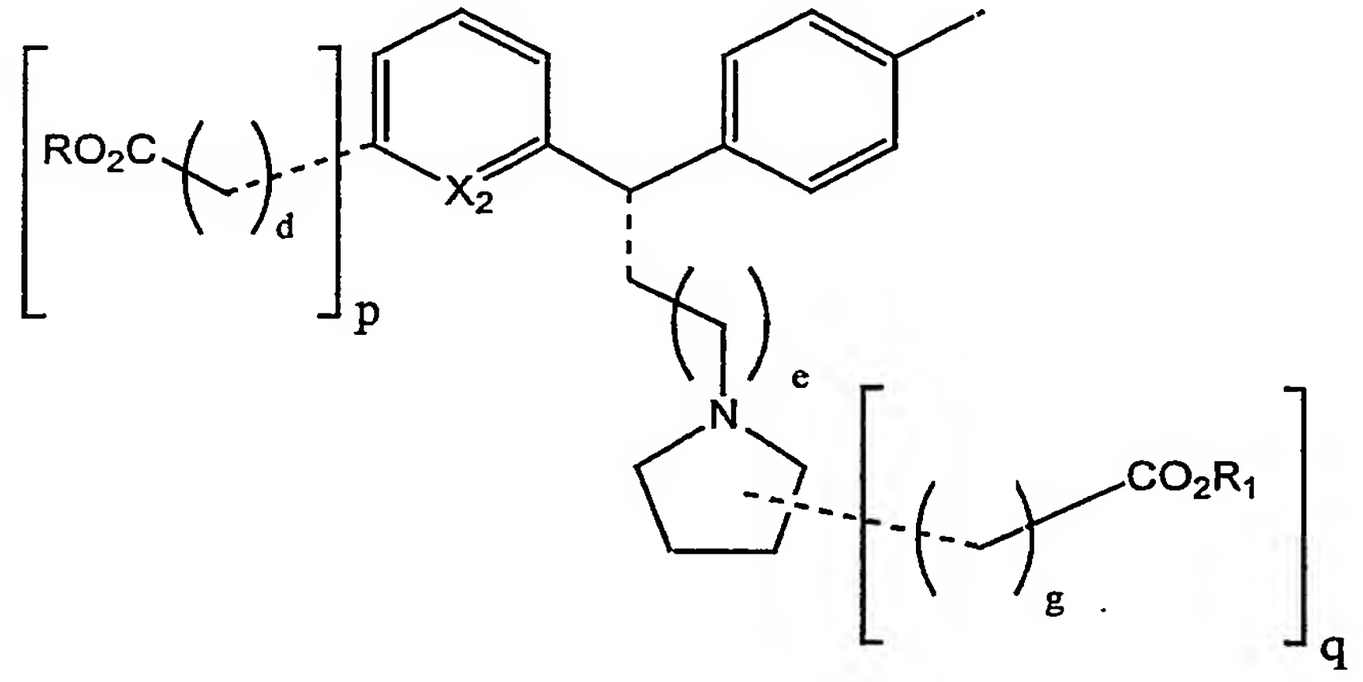
The language "doxepin-like compounds" is intended to include analogs of doxepine or antihistamines that include two aryl groups linked to the same atom that are linked through a tricyclic ring system, *e.g.* a seven membered ring (*i.e.*, similar to that of doxepine). In addition, doxepin-like compounds may posses a piperidine ring or the ring can be replaced by a linear structure, *e.g.*, an alkylene group (*i.e.*, similar to that of doxepine). In certain embodiments, the doxepin-like compounds are represented by Formula (VI):



(VI)

wherein the dashed line represents a single or double bond; R_1 and R_2 are substituents that are selected such that the compound can perform its intended function, *e.g.*, substituents that are described for antihistamines; X_1 is O, S, H, or CH_2 and n 1 to 6. In one embodiment, n is 1 to 4. In a specific embodiment, n is 1, 2, or 3.

The language "triprolidine-like compounds" is intended to include antihistamines that include two aryl groups linked to the same atom, not linked through a tricyclic ring system, and are distinguished by the presence of a pyrrolidine ring. In certain embodiments, the triprolidine-like compounds are represented by Formula (IV):

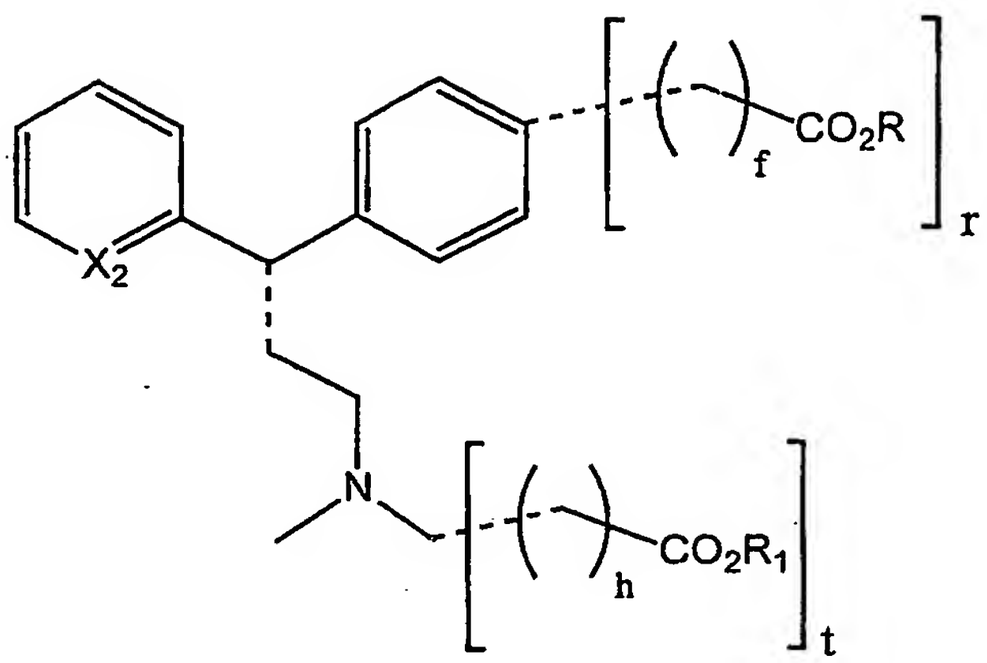


(IV)

wherein d = 0 through 5, e = 0 through 4, g = 0 through 5, the dashed line represents a single or double bond, R and R_1 are independently H or any group which imparts properties to the therapeutic compound to promote penetration into the CNS and to modify the half-life of the compound, and p and q are 0 or 1. In certain embodiments, p and q are not both 1. The $(CH_2)_m$ linker to the ester or carboxylic acid group, can be substituted with one or more substituents.

The language "acrivastine analogs" is intended to include the particular embodiment of Formula (IV), wherein the side chain that contains the CO_2R is an acrylate, *e.g.*, acrylic acid (as depicted in Scheme 1).

The language "pheniramine analogs" is intended to include antihistamines that include two aryl groups linked to the same atom, not linked through a tricyclic ring system. In addition, pheniramine analogs are distinguished by the presence of a dimethylamine moiety. In certain embodiments, the pheniramine analogs are represented by Formula (V):



(V)

wherein f = 0 through 5, h = 0 through 5, the dashed line represents a single or double bond, R and R_1 are independently H or any group which imparts properties to the therapeutic compound to promote penetration into the CNS and to modify the half-life of the compound, X_2 is CH or N, and r and t are 0 or 1. In certain embodiments, r and t are not both 1. The $(CH_2)_m$ linker to the ester or carboxylic acid group, can be substituted with one or more substituents.

An antihistamine of the instant invention may be substituted by one or more substituents, which are selected and positioned within the molecule such that the compound is able to perform its intended function. For example, the substituent(s) can be located on any available position, such as, the aryl rings, the spacer molecule, the drug activity modulating moiety, any branching moieties, or on other substituents. Exemplary substituents include substituted or unsubstituted alkyl, alkenyl, alkynyl, and aromatic or aryl moieties as defined herein. In particular, the antihistamines of the invention may be substituted by substituents including, but not limited to, hydrogen; halogen, *e.g.* bromide, chloride, or fluoride; dimethylaminocarbonyl; fluoroalkyl, *e.g.*, trifluoromethyl; hydroxy; alkyl, *e.g.*, C_{1-6} alkyl, *e.g.*, methyl or ethyl; alkoxy, *e.g.*, C_{1-6} alkoxy, *e.g.*, methoxy or propoxy; carboxylic acid; methylhydroxy; methylcarbonyl; cyano; aminomethyl; (aminoalkyl); ethoxycarbonylmethoxy; cyanomethyloxy; (acetoxyethyl)oxy; (hydroxyoxyethyl)oxy; morphilinoethyloxy; (tetrazol-5-yl)methyloxy; carboxymethyloxy; dimethylaminocarbonylmethyloxy; morphilinocarbonylmethyloxy; (1-ethoxycarbonyl-1-methylethyl)oxy; (1-carboxy-

1methylethyl)oxy; (2-methoxyethyl)oxy; (1-dimethylaminocarbonyl-1-methylethyl)oxy; (1-ethoxycarbonyl)cyclobutoxy; (1-carboxy)cyclobutoxy; (1;1-dimethyl-2-hydroxyethyl)oxy; (2;2-dimethyl-2-hydroxyethyl)oxy; acyloxy; cycloalkyl; arylalkyl; alkoxycarbonyl; and substituted or unsubstituted amines.

In certain embodiments, the aryl rings may be substituted with one or more substituents, each of which may be different or the same, and include, for example, hydrogen, halogens, alkyl, fluoroalkyl, *e.g.*, trifluoromethyl, hydroxy, alkoxy, and other substituents, such as, $--(O)_u --(CH_2)_t -C(O)OR_4$, $--(O)_u --(CH_2)_t --OC(O)R_4$, $--(O)_u --(CH_2)_t --C(O)--NR_5 R_6$ or $--(O)_u --(CH_2)_t --NHC(O)O--R_4$ wherein: t is an integer, such as an integer from zero to about three, and the methylene group $--(CH_2)_t --$ can be substituted or unsubstituted; and R_4, R_5 or R_6 are independently hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group. Alternatively, R_5 and R_6, taken together with the nitrogen atom to which they are bonded, can form a non-aromatic heterocyclic ring.

Suitable substituents on an aliphatic group, aromatic group (carbocyclic and heteroaryl), non-aromatic heterocyclic ring or benzyl group include, for example, an electron withdrawing group, a halogen, azido, cyano, fluoroalkyl, *e.g.*, trifluoromethyl, carboxylic acid, hydroxy, $--CONR_8 R_9$, $--NR_8 R_9$, $--OS(O)_2 NR_8 R_9$, $--S(O)_2 NR_8 R_9$, sulfonic acid, sulfonamide, guanidino, $--(O)_u --(CH_2)_t --C(O)OR_4$, $--(O)_u --(CH_2)_t --OC(O)R_4$, $--(O)_u --(CH_2)_t --C(O)--NR_5 R_6$, $--(O)_u --(CH_2)_t --NHC(O)O--R_4$, --Q--H, --Q-(aliphatic group), --Q-(substituted aliphatic group), --Q-(aryl), --Q-(aromatic group), --Q-(substituted aromatic group), $--Q--(CH_2)_p$ -(substituted or unsubstituted aromatic group), --Q-(non-aromatic heterocyclic group) or $--Q--(CH_2)_p$ -(non-aromatic heterocyclic group) wherein: p is an integer from 1-5; R_4, R_5 or R_6 are independently --H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a non-aromatic heterocyclic group, --NHC(O)--O-(aliphatic group), --NHC(O)--O-(aromatic group) or --NHC(O)--O-(non-aromatic heterocyclic group); R_5 and R_6, taken together with the nitrogen atom to which they are bonded, can form a non-aromatic heterocyclic ring; t is an integer from zero to about three; the methylene group, $--(CH_2)_t --$, can be substituted or unsubstituted; and Q is --O--, --S--, --S(O)--, $--S(O)_2 --$, $--OS(O)_2 --$, --C(O)--, --OC(O)--, --C(O)O--, --C(O)C(O)--O--, --O--C(O)C(O)--, --C(O)NH--, --NHC(O)--, --OC(O)NH--, --NHC(O)O--, --NH--C(O)--NH--, $--S(O)_2 NH--$, $--NHS(O)_2 --$, $--N(R_7)--$, $--C(NR_7)NHNH--$, $--NHNHC(NR_7)--$, $--NR_8C(O)--$ or $--NR_8 S(O)_2 --$ wherein: R_7 is hydrogen, an aliphatic group, a benzyl group, an aryl group or non-aromatic heterocyclic group; R_8 and R_9 are independently hydrogen, hydroxy, an aliphatic group, a substituted aliphatic group, a benzyl group, an aryl group or non-aromatic heterocyclic group; and u is zero or one.

A substituted non-aromatic heterocyclic ring, benzyl group or aromatic group can also have an aliphatic or substituted aliphatic group, as a substituent. In addition, a substituted aliphatic group can also have an oxo group, epoxy group, non-aromatic heterocyclic ring, benzyl group, substituted benzyl group, aromatic group or substituted aromatic group as a substituent. A substituted non-aromatic heterocyclic ring can also have =O, =S, =NH or =N(aliphatic, aromatic or substituted aromatic group) as a substituent. A substituted aliphatic, substituted aromatic, substituted non-aromatic heterocyclic ring or substituted benzyl group can have more than one substituent. Acyl groups include substituted and unsubstituted aliphatic carbonyl, aromatic carbonyl, aliphatic sulfonyl and aromatic sulfonyl. Suitable electron withdrawing groups include, for example, alkylimines, alkylsulfonyl, carboxamido, carboxylic alkyl esters, -CH=NH, -CN, $-NO_2$ and halogens.

In certain embodiments of the invention, the therapeutic compound has a favorable biological property. In one embodiment of the invention, the invention is a method of treating a sleep disorder. The method comprises administering an effective amount of an antihistamine compound, such that the sleep disorder is treated, wherein the antihistamine compound has a favorable biological property (FBP).

The language "favorable biological property (FBP)" includes one or more biological properties that allow the compound to perform its intended function in an enhanced manner. Examples of favorable biological properties include but are not limited to induction of a discrete sleep or hypnotic state, activity of the therapeutic compound for a discrete period of time, penetration through the blood brain barrier into the CNS, *e.g.*, resulting from lipophilicity of substituents or conformational lipophilicity (*i.e.*, lipophilicity as a result of a particular conformation, such as internal salt formation between a carboxylate anion and a protonated amine), modulation of the half-life of the therapeutic compound, *in vivo* hydrolysis of an ester by esterases that allows sequestration of the therapeutic compound in the CNS, an alteration of charge, an alteration of pharmacology-kinetics, an alteration of log P by a value of 1 or more, increased receptor selectivity, reduced peripheral half-life, the ability to increase dosage, increased peripheral elimination, decreased anti-muscarinic activity, decreased anti-cholinergic, and any combination thereof. It should be understood that the language "FPB" is intended to include a single property or a combination of two or more properties. In particular embodiments of the invention, the therapeutic compound induces a discrete sleep or hypnotic state by penetration into the CNS. In certain embodiments of the invention, the FBP includes increased concentration within the CNS for a discrete period of time as a result of a slower rate of conversion to the corresponding carboxylic acid by *in vivo* esterase activity within the CNS as compared with the periphery. In another embodiment of the invention, the FBP includes increased

concentration within the CNS for a discrete period of time as a result of the existence of an ionic bond that includes the carboxylate ion of the corresponding carboxylic acid, *e.g.*, zwitterion species formation with a nitrogen atom within the compound or salt bridge formation.

In certain embodiments, wherein the therapeutic compound is active for a discrete period of time, the FBP is a reduced ability of the subject to form a tolerance to the therapeutic compound. The language "tolerance" includes the natural tendency of a subject to become less affected by continued administration of a particular therapeutic compound due to repeated exposure to the compound. It should be noted that tolerance is typically increased coincident with the increased time that a compound is present in its active state within the subject. Reduced tolerance would coincide with increased therapeutic effectiveness.

The language "discrete sleep or hypnotic state" include a state of consciousness that is induced by the presence of active therapeutic compound of the invention, for a defined period of time. This is in contrast to the lingering hangover effect resulting from the existing treatments, *e.g.*, antihistamines, used for their sedative effect that maintain active drug concentrations for extended periods of time in the periphery.

The language "discrete period of time" includes a defined period of time in which the therapeutic compound is active, and depends upon the physical and reactive properties of the ester group. In one embodiment of the invention, the half-life of the therapeutic compound is 1 to 8 hours. In a preferred embodiment, the half-life of the therapeutic compound is 6 hours.

The language "sequestration" includes having enhanced concentration in the CNS and more rapid elimination from the periphery. The product of hydrolysis can exit the brain by various carboxylate excretion mechanisms, possibly at a slower rate than from the periphery producing a CNS sequestration of the carboxylate for a defined, or discrete, period of time. In one embodiment of the invention, elimination of the hydrolyzed carboxylate-containing metabolite occurs predominately by excretion though the kidneys, due to enhanced polarity of the metabolite, either as the free carboxylate or after Phase II further metabolism. In another embodiment, elimination occurs predominately by metabolism in the liver, *e.g.* hydrolysis of the ester followed by glucuronidation, and excretion into the bile. In certain embodiments, the brain assists in the elimination.

Another embodiment of the current invention is a method of modulating a sleep disorder target comprising administering to a subject an effective amount of a therapeutic compound, such that the therapeutic compound penetrates into the CNS and modulates the sleep disorder target, wherein the therapeutic compound is as described above and comprises any one of the following formulae:

[CA]-(SP)$_n$-[DA],

[CA]-(SP)$_n$-[EG],

[AD]-(SP)$_n$-[EG],

[AH]-(SP)$_n$-[DA], or

[AH]-(SP)$_n$-[EG]

wherein CA is a moiety that modulates an active CNS target receptor or a collection of active CNS target receptors, AD is a moiety that agonizes an adenosine receptor or a collection of adenosine receptors, AH is a moiety that antagonizes a histamine receptor or a collection of histamine receptors, DA is a drug activity modulating moiety that provides the ability to modulate the activity of the therapeutic compound, EG is an ester group that modifies the half-life of the therapeutic compound, SP is a spacer molecule, and n is 0 or 1.

In an additional embodiment, the invention is a CNS disorder target modulator comprising the formula:

[CA]-(SP)$_n$-[DA], or
[CA]-(SP)$_n$-[EG]

wherein CA is a moiety that modulates an active CNS target receptor or a collection of active CNS target receptors, DA is a drug activity modulating moiety that provides the ability to modulate the activity of the therapeutic compound, EG is an ester group that modifies the half-life of the therapeutic compound, SP is a spacer molecule, and n is 0 or 1.

Another embodiment of the invention is a sleep disorder target modulator comprising the formula:

[CA]-(SP)$_n$-[EG]

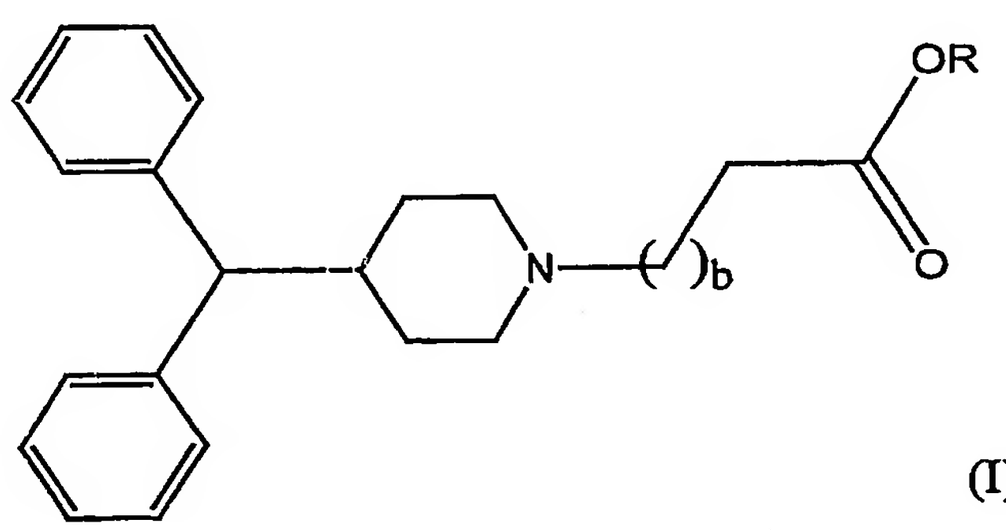
wherein CA is a moiety that modulates an active CNS target receptor or a collection of active CNS target receptors, EG is an ester group that modifies the half-life of the therapeutic compound, SP is a spacer molecule, and n is 0 or 1.

In a particular embodiment of the invention, a sleep disorder target modulator comprises the formula:

$[AH]-(SP)_n-[DA]$ or
$[AH]-(SP)_n-[EG]$

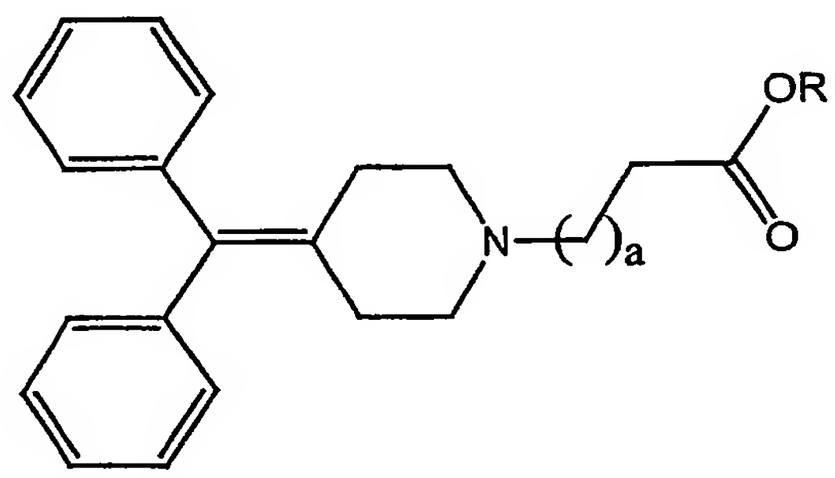
wherein AH is a moiety that antagonizes a histamine receptor or a collection of histamine receptors, DA is a drug activity modulating moiety that provides the ability to modulate the activity of the therapeutic compound, EG is an ester group that modifies the half-life of the therapeutic compound, SP is a spacer molecule, and n is 0 or 1.

In accord with the invention, particular embodiments of the pheniramine-like therapeutic compound used for treating CNS disorders, *e.g.*, sleep disorders, are:



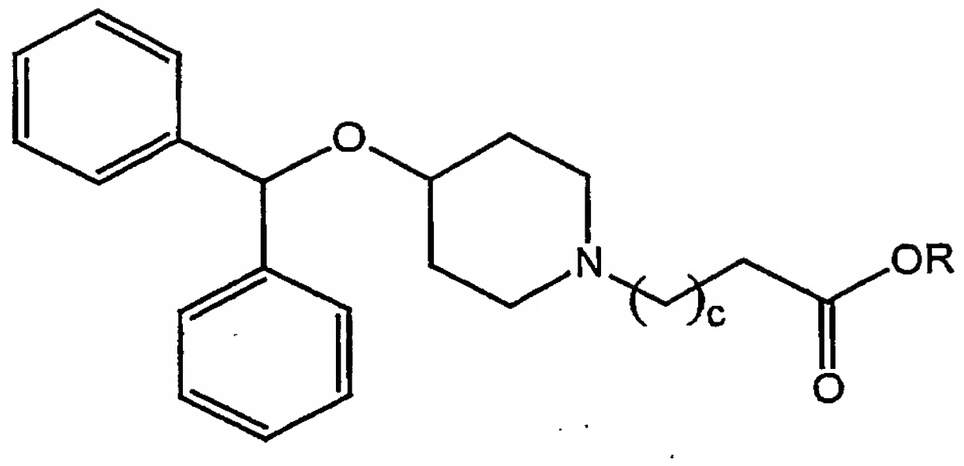
(I)

And



(II)

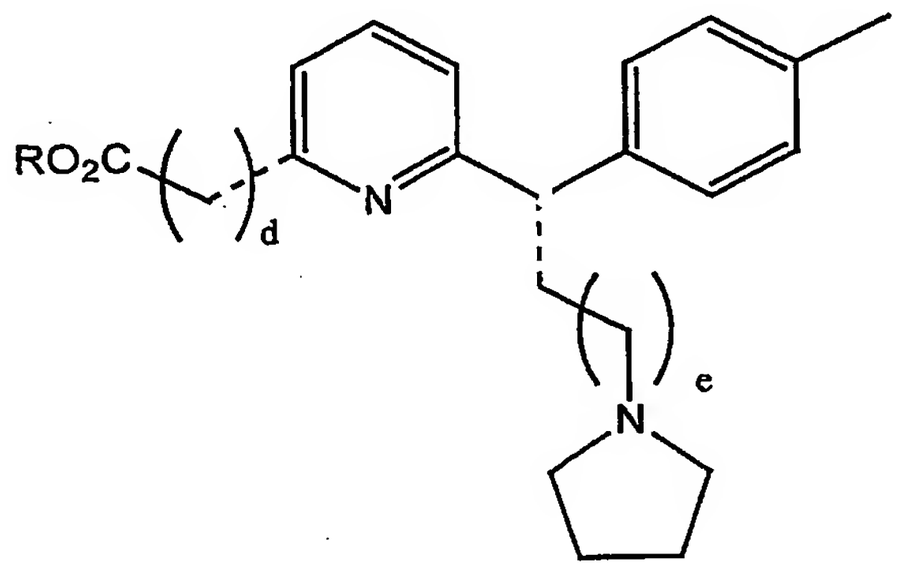
wherein a = 0 through 5, b = 0 through 5, and R is H or any group which imparts properties to the therapeutic compound to promote penetration into the CNS and to modify the half-life of the compound. In another embodiment of the therapeutic compound used for the treatment of a disorder, the diphenhydramine-like therapeutic compound is:



(III)

c = 0 through 5, and R is H or any group which imparts properties to the therapeutic compound to promote penetration into the CNS and to modify the half-life of the compound.

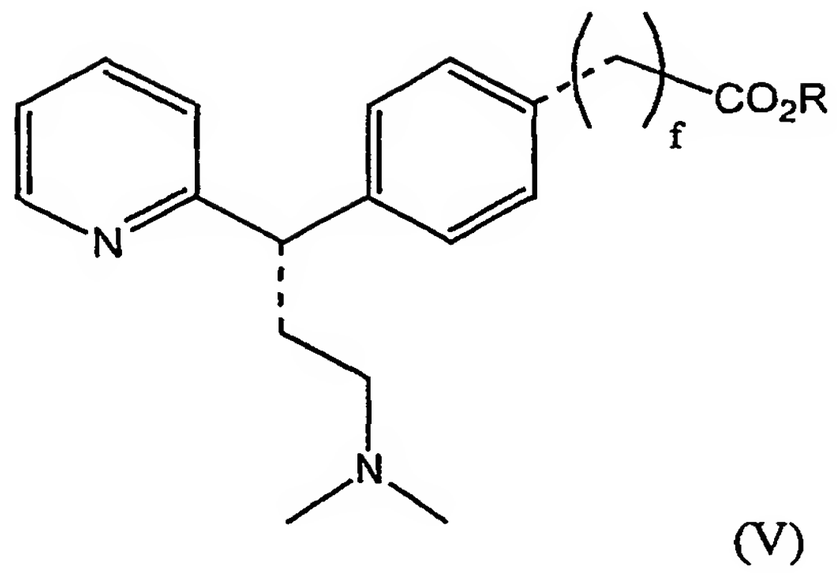
In another embodiment of the therapeutic compound used for the treatment of a disorder, the triprolidine-like therapeutic compound is:



(IV)

wherein d = 0 through 5, e = 0 through 4, the dashed line represents a single or double bond, and R is H or any group which imparts properties to the therapeutic compound to promote penetration into the CNS and to modify the half-life of the compound.

In another embodiment of the therapeutic compound used for the treatment of a disorder, the pheniramine analog therapeutic compound is:



(V)

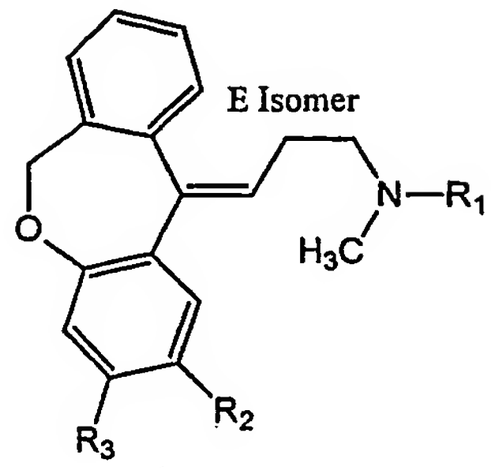
wherein f = 0 through 5, the dashed line represents a single or double bond, and R is H or any group which imparts properties to the therapeutic compound to promote penetration into the CNS and to modify the half-life of the compound.

In preferred embodiments of the invention, a = 0 or 1; b = 0 or 1; c = 0 or 1; d = 1 or 2; e = 1 or 2; and f = 1 or 2. In particular embodiments of Formulae (I), (II), (III), (IV), and (VI), R is a bulky ester.

In one embodiment, the compound of the invention is doxepin, pheniramine, diphenhydramine, triprolidine, or acrivastine.

An additional embodiment of the invention is the composition of several analogs of doxepin and acrivastine. The structures of several compounds, as well as their activity, are shown in Scheme 1. These compounds have demonstrated anti-H1 activity related to other antihistamine compounds of the invention.

SCHEME 1



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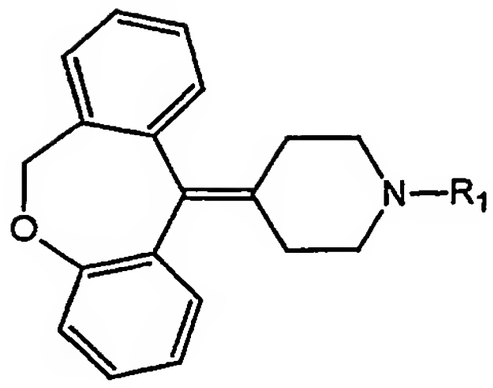
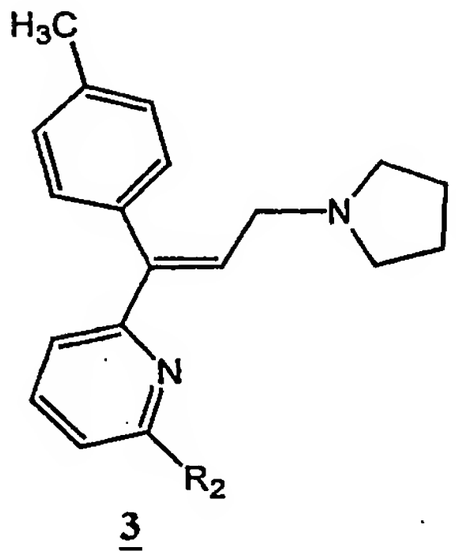


2



3

Acrivastine Analogs

Compd.	pA_2
3, R_2 = H	9.7
3, R_2 = CH=CHCO$_2$H	9.2

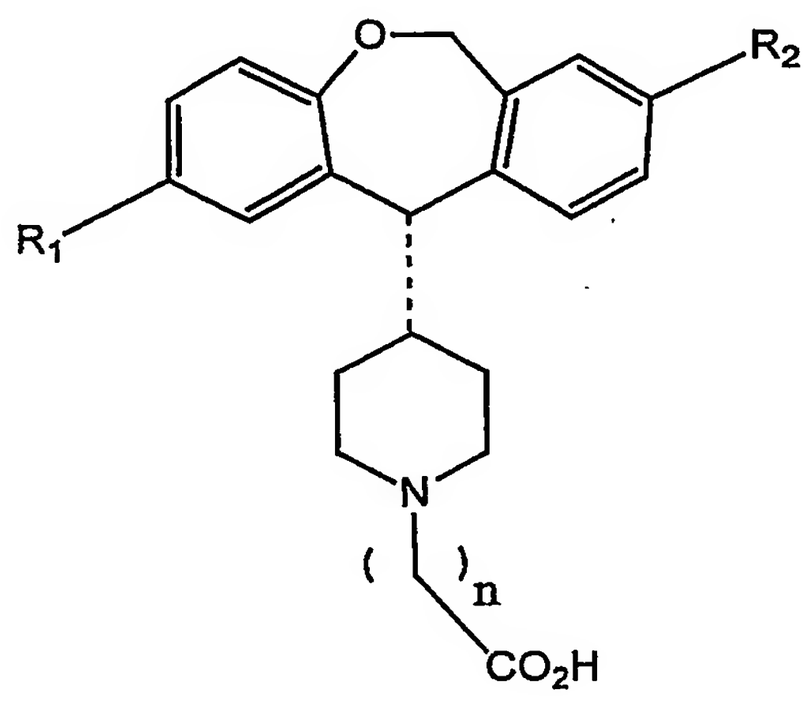
Doxepine Analogs[1,2,3]

(R = H unless shown otherwise)

Compd.	pK_B
1, R_1 = CH_3	10.11
1, R_1 = CH_2CO_2H	7.81
1, R_1 = $CH_2CH_2CO_2H$	8.51
	K_i (nM)
1, R_2 = CH_3	0.13
1, R_2 = CH_2CH_2OH	0.48
1, R_2 = CO_2H	4.2
1, R_2 = CH_2CO_2H	5.2
1, R_2 = $CH_2CH_2CO_2H$	4.2
1, R_2 = CO_2H (Z isomer)	20.0
1, R_3 = CO_2H (Z isomer)	24.0
	pIC_{50}
2, R_1 = CH_3	9.5
2, R_1 = $CH_2CH_2CO_2H$	6.5

References: 1) H. Muramatsu et al, Chem. Pharm. Bull. 41(11), 1987 (1993), 2) N. Iwasaki et al, Chem. Pharm. Bull. 42(11), 2285 (1994), 3) E. Ohshima, et al., J. Med. Chem. 35, 2074 (1992).

In particular embodiments of the invention, the doxepin-like therapeutic compound is represented by the following formula:



(VI)

wherein

the dashed line represents a single or double bond;

R_1 = H, OH, CH_2OH, CH_2CH_2OH;

R_2 = H, CH_3, CF_3, Cl, Br; and

n is 1, 2, or 3.

In certain embodiments, the R_1 substituents will alter the *in vivo* half-life of the drug. In certain embodiments, the R_2 substituents enhance the H1 receptor binding affinity. In addition, the spacer molecule, *e.g.*, the $(CH_2)_m$ linker to the carboxylic acid group, can be substituted with one or more substituents. In one embodiment, the spacer molecule is mono-substituted. In another embodiment of the invention, the spacer molecule is disubstituted. In particular embodiments, the linkers of the invention may be geminally-dialkylated, *e.g.*, gem-dimethylated, singly substituted with a substituent other than a noncyclic alkyl group, *e.g.*, a heteroatom, or a cyclic substituent wherein one or more of the carbons of the spacer molecule is contained in the ring, *e.g.*, heterocycle (*e.g.*, tetrahydrofuran or tetrahydropyran), or cyclic alkyl, *e.g.*, cyclopropyl. However, the substitution of the spacer molecule is independent of the substitution at the R_1 and R_2 positions.

In specific embodiments of the invention which are directed to doxepin-like compounds, such that when R_1 and R_2 are both H, the alkyl spacer molecule to the carboxylic acid is singly or doubly substituted with alkyl., including gem-dialkyl substitution, *e.g.*, gem-dimethyl substitution. In certain embodiments, the compound of the invention is not a doxepin-like compound of Formula (V), wherein the alkylene spacer molecule is unsubstituted, and R_1 and R_2 are selected from the group consisting of H, halogen CF_3, OH, $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkoxy. In another embodiment, R_1 and R_2 are not both H when the alkylene spacer molecule is unsubstituted. In one embodiment, n is not 2 or 3 when the spacer molecule is unsubstituted.

Another embodiment of the invention is a pharmaceutical composition comprising a therapeutic compound as prepared according to the methodology of this invention, and a pharmaceutically acceptable carrier.

In specific embodiments of the invention, the therapeutic compounds of the invention for treating CNS disorders, *e.g.*, sleep disorders, are selected from Table 2. In certain embodiments, the therapeutic compounds of the invention for treating CNS disorders, *e.g.*, sleep disorders, are selected from Table 3.